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Adult congenital heart disease:
long-term survival, arrhythmias, and emerging therapy

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Abbreviations

CI= Confidence interval

D-TGA= D-transposition of the great arteries

D-TGV= D-transposition des gros vaisseaux

HR= Hazard ratio

ICD= Implantable cardioverter-defibrillator

LR= Likelihood ratio

OR= Odds ratio

RF= Radiofrequency

RR= Risk ratio

SCD= Sudden cardiac death

VT= ventricular tachycardia

Dedication

To my wife Nadine, for her support, encouragement, patience, and love

Summary

Improvements in pediatric congenital heart disease have resulted in a rapidly expanding population of young adult survivors. Late complications include arrhythmias and sudden cardiac death (SCD). The following manuscripts address some issues encountered in adult congenital heart disease and electrophysiology:

1. Value of programmed ventricular stimulation after tetralogy of Fallot repair: a multicenter study. *Circulation* 2004; 109(16): 1994-2000.
2. Long-term outcomes after atrial switch for transposition of the great arteries: a meta-analysis comparing Mustard and Senning procedures. *Cardiol Young* 2004; *In Press*
3. Lower incidence of thrombus formation with cryothermal versus radiofrequency catheter ablation. *Circulation* 2003; 107(15): 2045-2050.

Programmed ventricular stimulation was performed in 252 patients with repaired tetralogy of Fallot followed for 18.5±9.6 years. Clinical ventricular tachycardia (VT) and/or SCD occurred in 24.6%. Adding sustained polymorphic VT to the definition of inducibility enhanced the diagnostic yield, with sensitivity 77.4% and specificity 79.5%. Event-free survival in non-inducible versus inducible patients at 1, 5, 10, and 15 years was 97.9%, 92.8%, 89.3%, 89.3% versus 79.4%, 62.6%, 58.7%, and 50.3%. Inducible sustained VT independently predicted subsequent clinical VT and SCD (RR 4.7).

The second manuscript focuses on patients with D-transposition of the great arteries (D-TGA). In a meta-analysis, long-term outcomes are compared among patients having had Mustard or Senning atrial switch procedures. Seven studies (885 patients) were included. A trend towards lower mortality was observed in Mustard (n=369) compared to Senning (n=474) patients (HR 0.63, p=0.130). Systemic venous obstruction was more common in Mustard patients (RR 3.5, $p<0.001$), with a trend towards more pulmonary venous obstruction in Senning patients. A trend towards fewer residual shunts but more sinus node dysfunction was observed in Mustard patients. Systemic heart failure and functional capacity were similar. Knowledge of these differences may facilitate risk stratification and follow-up.

Finally, radiofrequency (RF) catheter ablation has been successful in eliminating macroreentrant circuits in patients with congenital heart disease but may be complicated by clinical thromboembolic events. In a pre-clinical study, the third manuscript compares the thromboembolic potential of RF and cryoenergy ablation, a newer technology for the catheter-based treatment of arrhythmias. Catheter ablation was performed in 22 dogs at atrial and ventricular sites preselected by a randomized factorial design devised to compare RF with cryolesions. After 7 days, the incidence of thrombus was significantly higher with RF (75.8% versus 30.1%, p=0.0005). In a multiple regression model, RF remained an independent predictor of thrombus formation (OR 5.6, p=0.0042). Thrombus volume was significantly greater with RF compared to cryoablation (2.8 mm^3 versus 0.0 mm^3, $p<0.0001$). More voluminous thrombi were associated with larger RF lesions but cryolesion dimensions were not predictive of thrombus size. In conclusion, RF energy is significantly more thrombogenic than cryoenergy.

Key words: congenital heart disease, electrophysiology, arrhythmia, tetralogy of Fallot, ventricular tachycardia, sudden cardiac death, transposition of the great arteries, catheter ablation, cryoenergy, thrombus

Résumé

Les corrections apportées aux cardiopathies congénitales ont été la cause d'une augmentation rapide de la population de jeunes adultes survivants. Par contre, la présence de complications tardives incluent les arythmies et la mort subite cardiaque. Les manuscrits suivants posent certaines questions rencontrées en cardiopathie congénitale adulte et en électrophysiologie:

1. Valeur de la stimulation ventriculaire programmée chez des patients ayant subi une réparation chirurgicale pour tétralogie de Fallot: une étude multicentrique. *Circulation* 2004; 109(16): 1994-2000.
2. Résultats à long-terme de la transposition des gros vaisseaux suite à une intervention de détransposition à l'étage auriculaire: une méta-analyse comparant les procédures de Mustard et Senning. *Cardiol Young* 2004; *en impression (Juin)*
3. Incidence inférieure de formation de thrombus avec fulguration par cathéter cryothermal versus radiofréquence. *Circulation* 2003; 107(15): 2045-2050.

La stimulation ventriculaire programmée a été pratiquée chez 252 patients ayant subi une réparation complète d'une tétralogie de Fallot, dans une étude de cohorte multicentrique, avec un suivi de 18.5±9.6 ans. Une tachycardie ventriculaire clinique ou une mort subite cardiaque sont survenues chez 24.6% des cas. L'ajout de la tachycardie ventriculaire polymorphe soutenue à la définition d'inductibilité a amélioré la valeur diagnostique, avec une sensibilité de 77.4% et une spécificité de 79.5%. La survie sans événements chez les patients non-inductibles versus ceux qui étaient inductibles à 1, 5, 10, et 15 ans était de 97.9%, 92.8%, 83.3%, 89.3% versus 79.4%, 62.6%, 58.7%, et 50.3%. La tachycardie ventriculaire inductible soutenue était un

facteur de prédiction indépendant d'une tachycardie ventriculaire ou d'une mort subite subséquente.

Le deuxième manuscrit concerne plus particulièrement les patients atteints d'une D-transposition des gros vaisseaux. Une méta-analyse compare les résultats à long-terme obtenus chez des patients ayant subi la procédure de Mustard à ceux ayant subi la procédure de Senning. Sept études (885 patients) ont été incluses dans cette analyse. Une tendance vers une mortalité inférieure a été observée chez les patients ayant eu une chirurgie de Mustard (n=369) plutôt qu'une chirurgie de Senning (n=474) (HR 0.63, p=0.130). Une obstruction veineuse systémique était plus fréquente chez les patients ayant eu la procédure de Mustard (RR 3.5, p<0.001), par contre, une tendance vers plus d'obstructions veineuses pulmonaires fut observée chez les patients qui eurent la procédure de Senning. Chez les patients ayant eu la procédure de Mustard, une tendance vers moins de shunts résiduels mais plus de dysfonctions du nœud sinusal a été notée. L'insuffisance cardiaque systémique et la capacité fonctionnelle étaient similaires. Une connaissance de ces différences pourrait faciliter le suivi clinique et l'identification des risques de ces patients.

Finalement, la fulguration par cathéters avec radiofréquence (RF) peut éliminer des circuits de macro ré-entrées chez des patients avec cardiopathie congénitale, mais peut être compliquée par l'occurrence d'événements thromboemboliques. Dans une étude pré-clinique, le troisième manuscrit compare la formation de thrombus dans la fulguration avec RF à celle de cryoénergie, une nouvelle technologie pour le traitement des arythmies cardiaques. La fulguration a été effectuée chez 22 chiens à des sites auriculaires et ventriculaires prédéterminés par un plan factoriel randomisé destiné à

comparer la RF avec la cryo-fulguration. Sept jours après la fulguration, l'incidence de thrombus était plus élevée avec la RF (75.8% versus 30.1%, p=0.0005). Dans un modèle de régression multiple, la RF était un facteur de prédiction indépendant de la formation de thrombus (OR 5.5, p=0.0042). De façon statistiquement significative, le volume du thrombus était supérieur avec la RF comparativement à la cryo-fulguration (2.8 mm^3 versus 0.0 mm^3, p<0.0001). Des thrombus plus volumineux étaient associés à des lésions RF plus grandes, mais les dimensions des lésions créées par cryoénergie n'étaient pas un facteur de prédiction de l'étendue du thrombus. En conclusion, l'énergie par RF est significativement plus thrombogénique que la cryoénergie.

Mots clés: cardiopathie congénitale, électrophysiologie, arythmie, tétralogie de Fallot, tachycardie ventriculaire, mort subite cardiaque, transposition des gros vaisseaux, fulguration par cathéter, cryoénergie, thrombus

Introduction

Abnormal cardiovascular development accounts for a broad spectrum of heart disease with wide variability in clinical phenotype. Approximately 75 of 1000 live births are complicated by some form of cardiovascular malformation, 25% of which are considered moderate or severe.[1] Despite considerable advances over the last 50 years, congenital heart disease remains a major public health concern. Children with such anomalies are more likely to suffer from prolonged hospitalizations, multiple surgeries, disrupted physical, intellectual, or motor development, impaired quality of life, and decreased life expectancy.[2;3]

In cyanotic congenital heart diseases such as tetralogy of Fallot and complete (D-)transposition of the great arteries (D-TGA), shunting of systemic venous blood into the arterial circulation results in arterial oxygen desaturation, the degree of which is determined by the magnitude of right-to-left shunting. Without intervention, most children with cyanotic heart disease do not survive to adulthood.[4-8] Recent advances in pediatric cardiology and cardiac surgery have allowed many such children to thrive well into their adult years. Nevertheless, as a result of hemodynamic or hypoxic stress imposed by the original congenital defect and postoperative sequelae from reparative surgery, electrophysiologic abnormalities that are sometimes life-threatening may hinder long-term survival.[9] This thesis explores and elucidates matters regarding long-term outcomes, risk stratification, and therapies germane to the emerging subspecialty of cardiology where adult congenital heart disease and electrophysiology intersect.

In the first manuscript, the value of programmed ventricular stimulation in identifying patients at risk for ventricular tachycardia (VT) or sudden cardiac death

(SCD) is assessed in a multicenter cohort study of patients with tetralogy of Fallot, the most common cyanotic heart disease in adults. The second study focuses on patients with D-TGA. In a meta-analysis, long-term outcomes including overall survival and arrhythmic complications are compared among patients having had Mustard or Senning atrial switch procedures in childhood. Finally, macroreentrant arrhythmic circuits are well recognized in patients with repaired tetralogy of Fallot and atrial baffle procedures for D-TGA. Radiofrequency (RF) catheter ablation has been successful in eliminating further episodes of atrial reentrant tachycardia in patients with Mustard or Senning procedures and VT after tetralogy of Fallot repair. However, particularly in procedures requiring extensive ablation lesions such as for congenital heart disease, thromboemboli may complicate RF ablation. In such high-risk substrates as ventricular tachycardia, the reported incidence of clinical thrombomboli is 2.8%.[10] In a pre-clinical study, the third manuscript compares the thromboembolic potential of RF and cryoenergy ablation, a newer technology for the catheter-based treatment of arrhythmias.

Tetralogy of Fallot

Tetralogy of Fallot is the most common cyanotic heart disease beyond infancy, accounting for approximately 10% of all congenital heart malformations.[11] While its etiology is unknown, it is considered a conotruncal septation defect resulting from embryologically abnormal ectomesenchymal tissue migration.[12] An underdeveloped subpulmonary infundibulum gives rise to right ventricular outflow tract obstruction and an aorta that overrides a malaligned usually large nonrestrictive subpulmonic ventricular septal defect displaced antero-superiorly.[13] Right ventricular hypertrophy develops as a consequence of pulmonary obstruction. "Corrective" surgery consists of closing the ventricular septal defect, relieving the right ventricular outflow tract obstruction, and repairing associated anomalies.

Ventricular tachycardia and sudden cardiac death

Intracardiac repair of tetralogy of Fallot has been performed for over 40 years with excellent results.[14;15] However, SCD has consistently been found to be the single most common cause of mortality late after repair.[16-20] In 1997, Nollert et al.[17] reported long-term survival post tetralogy of Fallot repair, excluding patients who died within the first post-operative year. In 490 patients, actuarial survival rates were 97%, 94%, 89%, and 85% at 10, 20, 30, and 36 years, respectively. A larger multicenter cohort of 793 patients with corrected tetralogy of Fallot was published more recently.[18] After the first 5-10 years following surgery, a small but steady decline in freedom from VT and SCD was observed with 11.9% and 8.3% experiencing documented clinical VT and SCD, respectively, by 35 years.

Given the small but undeniable risk of ventricular arrhythmias and SCD post tetralogy of Fallot repair, considerable efforts have been directed towards identifying predictors allowing stratification of patients into high and low-risk categories. In the largest cohort study to date[18] that combined six hospital databases with a mean follow-up of 21.1 years, independent risk factors for sustained VT were QRS interval ≥180 ms [RR 8.76, 95% CI (2.36-32.6)] and an annual increase in QRS duration [RR 1.08 for each 1 ms increase/year, 95% CI (1.04-1.10)]. Early lengthening of the QRS interval post tetralogy of Fallot repair results from surgical injury to the right bundle branch and myocardium,[21] whereas later broadening reflects right ventricular dilation.[22;23]

In addition to QRS duration and its rate of change, independent predictors of SCD included older age at repair [RR 1.08, 95% CI (1.02-1.15)] and presence of a transannular right ventricular outflow tract patch [RR 11.7, 95% CI (1.33-103.1)]. Patients with VT or SCD were more likely to have increased cardiac-thoracic ratios, at least moderate pulmonary and tricuspid regurgitation, and peripheral pulmonary stenosis. A higher QT dispersion was also noted, believed to reflect increased heterogeneity in myocardial repolarization. Other reported risk factors have included frequent ectopic beats,[24] increased right ventricular systolic pressures,[20;25;26] complete heart block,[20;27] and increased JT dispersion.[28;29]

Programmed ventricular stimulation

Little is known about the predictive value of programmed ventricular stimulation in risk stratifying patients post tetralogy of Fallot repair. Attempts to clarify its utility have been limited by small numbers of adequately studied reported patients and the infrequent occurrence of VT and SCD on follow-up.[30-34] When monomorphic VT is inducible, it is macroreentrant in nature with the greatest conduction delay often situated in the subinfundibular isthmus.[35] The wavefront of propagation commonly rotates either clockwise or counterclockwise around myotomy scars or surgical patches. Successful ablation sites have included the subinfundibular isthmus and inferior margin of the ventricular septal defect patch.[24;35-49] While case-reports and small case series suggest a high rate of acute success by RF[35;36;42-49] and cryosurgical ablation,[24;37-41;50] the incidence of recurrent VT is unknown and the impact on prevention of SCD undefined. In nine patients with clinical VT and surgical reintervention consisting of cryoablation and pulmonary valve replacement, none recurred at a mean follow-up of 4.7 years.[50]

Marie et al.[32] reported a positive association between inducible sustained VT and right ventricular dimensions. The same center later reported a series of 89 consecutive patients with repaired tetralogy of Fallot who underwent electrophysiologic testing from 1980 to 1996.[33] Average age at time of testing was 10.9±6.5 years. Stimulation was performed with three extra beats (S1, S2, S3, S4) in sinus rhythm and with eight-beat pacing trains of 462 ms and 400 ms at the right ventricular apex and outflow tract with and without isoproterenol to increase heart rates by 30 to 50%. Burst pacing was also performed at cycle lengths of 400 to 250 ms. Positivity was defined as sustained monomorphic VT (i.e. lasting more than 30 seconds or requiring electrical cardioversion). Overall, 24% of patients were inducible, all of whom required at least two extrasystole. Over the 8.3±4.9 years of follow-up, four patients developed clinical VT and one suffered SCD. The authors concluded that the low clinical event rate precluded meaningful estimates of the predictive value of electrophysiologic testing. Independent predictors of inducible VT were older age at time of testing, previous palliative surgery, increased right ventricular systolic pressure, and symptoms of palpitations, presyncope, or syncope.

In a chapter on risk stratification post tetralogy of Fallot repair, Gatzoulis et al.[34] described a subset of 91 of 793 patients from the multicenter cohort[18] who underwent programmed ventricular stimulation. Patients were 24±11 years old at time of testing.

Indications included investigation of symptoms (88%), ventricular arrhythmias found on Holter monitoring (6%), "routine" follow-up testing (4%), and ablation of previously documented VT (2%). Sustained monomorphic VT was induced in 35%, with hemodynamic compromise in all. Predictors of inducible VT included longer duration of follow-up, wider QRS duration, increased QT dispersion, and peripheral pulmonary stenosis. The ability of electrophysiologic testing to predict subsequent clinical VT or SCD could not be estimated from the reported data.

In a series of 140 selected patients with congenital heart disease who underwent ventricular stimulation studies,[51] 33% (n=43) had tetralogy of Fallot. All electrophysiologic studies were performed in the drug-free state with stimulation protocols involving up to triple extrastimuli following a drive train at a minimum of two cycle lengths between 400 and 600 ms. Isoproterenol was administered in 42% of studies at a dose titrated to achieve 20%-30% decrease in resting cycle length. Overall, sustained VT was inducible in 25% of patients. In multivariate analysis, a positive ventricular stimulation study was associated with a sixfold increased risk of decreased survival and a threefold increased risk of serious arrhythmic events. A sensitivity of 87% in predicting mortality was observed, with a 33% rate of false-negative studies. However, subgroup analysis of only tetralogy of Fallot patients was not performed.

Despite the many clinical, electrocardiographic, and echocardiographic predictors of VT and SCD, efforts to reliably identify a high-risk subgroup with sufficient accuracy to guide management decisions regarding preventive therapy have had limited success. The value of programmed ventricular stimulation in this regard is currently unknown. The macroreentrant nature of induced ventricular arrhythmias circulating around scar tissue may be analogous to the substrate post-myocardial infarction in whom ventricular stimulation studies are of proven utility for risk stratification, identifying those most likely to benefit from ICD implantation. Clarifying the role of programmed ventricular stimulation may help guide physicians faced with the often daunting task of risk stratifying patients post tetralogy of Fallot repair in whom optimal strategies to prevent SCD are currently undefined.

D-Transposition of the Great Arteries

Complete transposition of the great arteries is responsible for 5% to 7% of all congenital cardiac malformations, occurs in 20 to 30 per 100000 live births, and has a strong male predominance.[11] In D-TGA, atria are concordant with their respective ventricles, i.e. the right atrium connects to the morphologic right ventricle, but the ventriculo-arterial alignment is discordant, i.e. the right ventricle gives rise to the aorta and left ventricle to the pulmonary artery. The exact etiology of the abnormal ventriculo-arterial relationship is currently unknown. Roughly two-thirds of patients have no major associated anomalies ('simple' D-TGA) whereas one-third have additional ventricular septal defects and/or pulmonary or subpulmonary stenosis ('complex' D-TGA).

In the absence of intracardiac mixing of systemic and pulmonary venous return, D-TGA results in two parallel circulations and is associated with over 90% mortality in the first year of life.[52] Thus, nearly all adults with D-TGA will have undergone some intervention. Although arterial switch surgery[53] is now the procedure of choice in many centers, it initially carried an unacceptably high mortality rate. Therefore, the large majority of adults with D-TGA have had intraatrial baffle repairs that redirect venous return. The Senning and Mustard procedures were derived independently and differ in technical detail but both achieve physiologic correction with a right ventricle that continues to support the systemic circulation. There are varying opinions on which atrial switch procedure is most effective.

Senning procedure

The Senning procedure was first introduced in 1959 as a means of redirecting systemic and pulmonary venous return without using grafts or prostheses.[54] In part due to its surgical complexity, it did not gain widespread acceptance until several years after its introduction. Essentially, a right atriotomy is created in front and parallel to the caval veins and extended to the atrial appendage. This exposes atrial septum that is subsequently incised anteriorly, superiorly, and inferiorly to form a large septal flap. The flap remains fixed posteriorly between the caval entrances. An incision between the coronary sinus and left atrium may or may not be performed to provide a large posterior border to suture the inferior septal flap and direct coronary sinus return to the newly formed systemic venous chamber. The systemic venous return conduit to the mitral valve is formed posteriorly by the retropositioned septal flap. Suturing the posterior atrial free wall flap to the anterior septal limbus completes the anterior portion of the conduit. A long left atriotomy is created in the internal atrial groove, exposing the right pulmonary veins. The pulmonary venous chamber pathway to the tricuspid valve is completed by suturing the anterior right free wall atrial flap over the right pulmonary veins to the anterior ridge of the left atriotomy. Thus, systemic venous return flows through the cavae and newly created atrial tissue conduit towards the mitral valve. Pulmonary venous return percolates into the neo pulmonary venous atrium and flows behind, to the right, and anterior to the systemic venous chamber towards the tricuspid valve.

Mustard procedure

In 1964, Mustard described an alternate technique for creating an intraatrial baffle using a pericardial patch.[55] A longitudinal incision is made in the right atrium. A large portion of the atrial septum is excised, leaving a medial septal ridge. The coronary sinus may or may not be cut back into the left atrium. A pericardial or synthetic baffle is sutured in place, like a pair of trousers with legs that encircle the orifices of superior and inferior vena cavae, thereby diverting caval venous return to the mitral valve. Pulmonary venous return is then directed towards the tricuspid valve.

Long-term complications

Although intraatrial baffle procedures have provided excellent short-term results and improved long-term survival, it was promptly recognized that despite physiologic repair, important residues and sequelae remained. The systemic right ventricle may fail, baffles may leak and/or become obstructed, and pulmonary venous return may become compromised. Moreover, arrhythmic complications including sinus node dysfunction, atrial tachyarrhythmias, and SCD may occur years after surgery.[56] The sinus node may be inadvertently destroyed or damaged by direct trauma as manifested by tissue hemorrhage; suture material may be placed near or through the sinus node; chronic fibrosis may occur; or the sinus node artery may be severed resulting in acute ischemia.[57] Venous cannulation for cardiopulmonary bypass also appears to be associated with a higher incidence of sinus node dysfunction compared to deep hypothermia.[58]

In the largest cohort study following an atrial switch procedure for D-TGA, 478 patients that survived the perioperative period after a Mustard repair were followed for an average of 11 years.[59] Bradyarrhythmias increased steadily over time. The actuarial rate of loss of sinus rhythm was 39% at 10 years and 60% at 20 years. Atrial flutter occurred in 14% and ectopic atrial tachycardia in 1%. The actuarial rate of atrial flutter 20 years after repair was 24%.

The most common cause of late mortality after an intraatrial baffle for D-TGA has consistently been reported to be SCD.[59-65] The pathogenesis is ill-defined and likely to be multifactorial. Although bradyarrhythmias are well described, the late peak in risk of SCD may be related to atrial tachyarrhythmias that conduct rapidly to the ventricle[66;67] or, alternatively, to primary ventricular arrhythmias in the context of progressive systemic ventricular dysfunction.[61;68] Loss of coordinated atrial activity and rapid ventricular rates can result in severe symptoms and hemodynamic compromise. Development of atrial arrhythmias is also associated with impaired ventricular function[69;70] and increased risk of SCD in some, but not all, studies.[71] In managing such patients, attempts to maintain sinus rhythm are usually warranted due to poor hemodynamic tolerance. Potential proarrhythmic effects of antiarrhythmic drugs should be monitored. Catheter ablation of atrial reentrant circuits can be effective but often requires access to the tricuspid valve isthmus on the pulmonary venous side of the circulation.[72] Implantable cardioverter defibrillators may be indicated in patients deemed high risk as a result of symptoms[66] and/or inducible ventricular arrhythmias.[68]

Mustard versus Senning

Reports have yielded conflicting results as to whether the type of atrial reconstruction, i.e. Mustard or Senning, is associated with different risks regarding specific complications and overall survival. Proponents of the Senning procedure advance that minimal, if any, nonviable tissue or prosthetic material favors future growth and optimizes atrial function, with potential reduction in pathway obstruction and arrhythmias.[73-75] Supporters of the Mustard procedure have claimed lower mortality, reduction in systemic and pulmonary venous obstruction, and decreased incidence of arrhythmias.[76] Comparative studies have not been performed.[56;77-79]

Catheter Cryoenergy Ablation

Since its introduction in the mid-1980s as an experimental treatment for cardiac arrhythmias, RF catheter ablation has become the procedure of choice for a wide variety of clinical arrhythmias. Although the extent of coagulation and tissue necrosis induced by RF energy depends on a variety of factors, hyperthermia-induced cell necrosis invariably involves destruction of endothelial and deeper layers with a small but inherent risk of aneurysmal dilatation, myocardial perforation, and thromboembolic events. Over the past two decades, hypothermic energy has been used for arrhythmia surgery. Theoretical advantages include preservation of underlying tissue architecture and a lower propensity for thrombus formation. Percutaneous cryoablation catheters have recently been devised permitting cryoenergy catheter ablation to emerge as a promising alternative to RF ablation.

Mechanism of cryoenergy ablation

Tissue-freezing temperatures are brought into contact with the endocardial surface by means of a percutaneous steerable catheter with the intent of rendering inactive all cells within a targeted area. Although the exact mechanism of cell death is debated, cellular destruction occurs through three phases: freeze/thaw, hemorrhage and inflammation, and replacement fibrosis.[80]

In the freeze/thaw phase, ice crystals are formed as cells are rapidly cooled to below zero temperatures. Crystals initially appear in the extracellular matrix due to a greater number of nucleation sites[81] and subsequently form intracellularly. Size and density of ice crystals relate to cryoenergy source proximity, tissue temperatures, and cooling rates. In and of themselves, these crystals do not seem to disrupt cell membrane integrity but compress and deform adjacent nuclei and cytoplasmic components,[82;83] beginning with mitochondrial damage.[84-86] Subsequent warming, referred to as "thawing", is integrally implicated in the cryodestructive process.[81;87-89] A[88]s cells warm, small high-energy intracellular crystals enlarge and conglomerate into larger damaging crystals.

Hemorrhage[90] and inflammation[85] occur withing 48 hours of thawing and characterize the second phase of tissue destruction.[80] The osmotic equilibrium initially disturbed by ice crystal formation is reestablished as water gradually migrates out from intracellular myocardial cells, resulting in an intracellular hyperosmotic state that damages cell membranes.[87] Restoration of the microcirculation to previously frozen tissue results in edema and circumscribed ischemic necrosis. Finally, replacement fibrosis occurs within weeks of the initial insult, resulting in a well-circumscribed dense lesion.[91]

Early beginnings

Following the creation of an automated cryosurgical apparatus cooled by liquid nitrogen in the early 1960s,[92] cryoenergy was used to treat various pathologies including cutaneous, gynecologic, prostatic, hepatic, ophthalmologic, neurosurgical, and oncologic disorders.[88;93-96] In 1948, Has el al. first described the production of controlled predictable homogeneous sharply demarcated myocardial lesions with cryoenergy using carbon dioxide (Table 1).[97;98] Transmural lesions were not complicated by rupture or aneurysmal dilation and no intracardiac thrombosis was seen. Maintenance of an intact tissue ultrastructure was later attributed to the resilience of collagen and fibroblasts to hypothermal injury.[85] Cryoenergy was first applied to cardiac conduction tissue in 1964 by Lister and colleagues[99] by suturing a 4-mm tube to the atrial septum near the bundle of His. A cooling mixture comprised of alcohol and carbon dioxide inhibited sinus node activity at -10^{0}C to -20^{0}C. Cooling of the atrioventricular node resulted in progressive PR prolongation and 5:1 block at -45^{0}C. Soon after terminating the cryoapplication, AV conduction returned to its baseline state.

Animal experiments with transcatheter cryoenergy ablation

The first animal experiment with transvenous cryoablation was reported by Gillette et al. in 1991,[100] with complete heart block induced in five swine. Through an 11-French cryocatheter cooled by pressurized nitrous oxide, cryothermia was applied for three minutes and repeated up to three times until a successful lesion was produced. Four of five swine maintained complete AV block for one hour and one had 2:1 AV block. Sharply demarcated hemorrhagic lesions were produced acutely. Two years later, the same group of investigators reported the histology of chronic six-week lesions in eight pigs.[101] Successive three minute applications at -60°C were applied to the AV junction by 8 or 11-French cryocatheters; AV block was maintained in five of eight animals at six weeks, and discrete dense lesions with no signs of inflammation or thrombus formation were noted.

Table 1. Transcatheter cryoenergy ablation: historical landmarks

Year	Authors	Contribution
1948	Hass and Taylor[97]	Cryoenergy applied to myocardium
1963	Cooper[92]	Cryosurgical apparatus developed
1964	Lister and Hoffman[99]	Application of cryoenergy to conduction tissue
1977	Harrison et al.[85]	Hand-held probe for cardiac cryosurgery
1991	Gillette et al.[100]	Transcatheter cryoablation in animals
1998	Dubuc et al.[102]	Cryocatheter made steerable and equipped with recording and pacing electrodes
1999	Dubuc et al.[103]	First transcatheter cryoablation in man

Although these initial studies demonstrated the feasibility of transcatheter cryoablation, catheter size, lack of steerability, and absence of cryocatheter recording electrodes were limiting factors. Cryolesion placement was guiding by a second catheter with electrode recording capabilities. In 1998, the first animal experiment using a steerable cryocatheter with recording and pacing electrodes was reported.[102] A 9-French cryocatheter with a 4-mm electrode tip and Halocarbon 502 as a refrigerant was used to create ventricular lesions in six dogs. Temperatures warmer than -30°C did not result in histologically identifiable lesions. Again, the sharply demarcated hemorrhagic lesions showed no evidence of thrombus formation. In two dogs, reversible ice mapping of the AV node was performed. With the cryocatheter positioned at the level of the AV node, the temperature was progressively lowered until high grade AV block or >50% PR interval prolongation was achieved. In both cases, 1:1 AV conduction resumed seconds after terminating the cooling process with no histological evidence of lesion formation.

Electrophysiologic parameters and cryomapping at -40°C were studied more extensively in a subsequent experiment in dogs.[91] Sinus cycle length, AH interval, HV interval, Wenckebach cycle length, and effective AV node refractory period measured before, 20 minutes, 60 minutes, and up to 56 days after cryoenergy mapping were not significantly different.

Finally, chronic catheter cryoablation lesions were later characterized in nine mongrel dogs sacrificed three and six weeks after cryoenergy ablation in right and left ventricles.[91] A mean temperature of -55°C created well-demarcated stable lesions with no evidence of thromboemboli. Similar results were reported using 8.5-French cryocatheters in 6 dogs[104] and 7 pigs.[96]

Transcatheter cryoenergy versus RF ablation

Transcatheter cryoablation appears to offer several potential advantages compared to RF energy (Table 2). Adhesion of the distal cooling electrode to underlying tissue affords greater catheter stability in the beating heart. This may be particularly advantageous in areas where contact is difficult to maintain or where minor inadvertent catheter movements may injure normal conduction tissue.[102;103] Secondly, cryolesions are more homogeneous with clearer and smoother demarcations from underlying normal myocardium.[102;104] In contrast, RF lesions have rougher more ragged edges that may be more susceptible to pro-arrhythmia as border zones with damaged yet viable cells may be at higher risk of undesired depolarisations.[91;104] T[91]hirdly, lesion size and shape are more predictably controllable with cryoenergy ablation by adjusting parameters in the freezing process.[105] Larger lesions, for example, may be produced by increasing the surface area of the catheter tip in contact with the endocardium or lowering the temperature at the catheter tip.[106]

Other hypothesized advantages include the tendency for scar not to rupture or form aneurysms,[103;107] and maintenance of ultrastructural tissue integrity.[108-110] Moreover, the desired substrate may by accurately mapped prior to definitive ablation. At sublethal temperatures, a functional effect is obtained with complete recovery to baseline electrophysiological properties and no histologically identifiable damage.[91;102] This may be particularly advantageous when arrhythmogenic substrates are located near critical sites such as the AV node. Also, ice ball formation may be visualized by ultrasonography thereby providing a continuous real-time image of the freezing process.[88] Intracardiac imaging by intravascular ulrasonography may confirm appropriate contact between the catheter tip and endocardium[91;103] and may ultimately reduce fluoroscopy exposure time.

Table 2. Advantages of cryoenergy compared to RF ablation

Advantages	Clinical Implications
Adhesiveness to endocardial tissue	Greater catheter stability
Homogeneous sharply demarcated lesions	Non-arrhythmogenic
	More controllable lesion depth and volume
Non-thrombogenic	Decreased risk of embolization
Reversible suppression of conduction tissue	Predict successful site
	Avoid unwanted lesions
	Ablation of high risk substrates
	Possible use in AV nodal modification
Visualization by ultrasound	Real-time monitoring
	Confirm endocardial contact
	Define optimal freezing parameters

Finally, RF is associated with a clinical thromboembolic complication rate of 0.6% to 0.8%.[10] This rate further increases when RF ablation is performed in systemic cardiac chambers (1.8% to 2.0%) and for ventricular tachyarrhythmias (2.8%), as is sometimes the case in congenital heart disease. Although not previously formally studied, preliminary data suggests that hypothermic tissue injury induced by cryoenergy ablation is less thrombogenic.

Overview of Methodology

The study designs and research methodology employed in the articles that comprise this thesis are intentionally varied. The first is a multicenter retrospective cohort study, the second a systematic review and meta-analysis, and the third a randomized pre-clinical experimental study.

In the first article, a cohort of individuals with tetralogy of Fallot and prior programmed ventricular stimulation studies from eight participating centers was identified. The exposure status was defined as the response to programmed ventricular stimulation categorized into one of three groups: inducible monomorphic VT, inducible polymorphic VT, and negative. As exposure was established from information recorded at some time in the past, the study is considered retrospective in nature. The primary outcome, a composite of clinical sustained VT and SCD, is determined from time of exposure until the study termination date, loss to follow-up, or death from other causes.

An essential feature of analyzing cohort data is accounting for the time at risk for the outcome of interest that is contributed by individuals while under observation. As a key component of this analysis, a multivariate Cox proportional hazard model[111] was used to compare rates of VT or SCD in patients with positive and negative programmed ventricular stimulation studies. This method assumed that the primary outcome in the population from which the cohort was sampled depended on a continuous time variable. It also allowed taking into account a number of potential confounders, including clinical, surgical, hemodynamic, electrocardiographic, and radiographic variables.

The second article is a systematic review and meta-analysis of observational studies. It addresses the research question of whether outcomes differ after Mustard versus Senning procedures for D-TGA. A search strategy was developed, including a systematic query of MEDLINE and EMBASE databases. Inclusion and exclusion criteria were made explicit. A strategy to assess study quality was detailed, and included a "component approach" where the importance of individual quality domains and direction of potential biases associated with such domains were examined with meta-regression analyses.[112] Relevant variables were extracted by two independent reviewers. Data were analyzed and heterogeneity was assessed. A decision to proceed with a random effects model, as opposed to a fixed effects model, was based on pre-defined criteria that assessed between study variation. A summary parameter was calculated for the primary outcome measure, i.e. a hazard ratio comparing overall survival in patients with Mustard versus Senning procedures. Potential publication bias was explored with Begg's funnel plot and by charting standardized effect versus precision. Limitations were discussed and conclusions provided.

The third study employs an experimental design in mongrel dogs. The exposure variable is allocated in a randomized fashion by the investigator. Each cardiac chamber (i.e. right atrium, right ventricle, and left ventricle) was randomly assigned a particular ablation setting, to compare RF ablation and cryoenergy ablation with configurations of varying sizes (7-French and 9-French), cooling rates (-1°C/s, -5 °C/s, and -20 °C/s), and target temperatures (-55°C and -75 °C). The animals were sacrificed seven days post-ablation. Personnel blinded to treatment modality performed morphometric analyses of the lesions. Primary outcome variables were the presence or absence of thrombus formation on the surfaces of ablation lesions and overall thrombus volumes. Statistical analyses respected the non-independent nature of the data structure, given that several ablation lesions were created in each animal. General estimating equations (GEE) in SAS were used to produce multiple regression marginal models for cluster sampling data by specifying link and distribution functions.

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Author contribution

As first author of the manuscript entitled, "Value of programmed ventricular stimulation after tetralogy of Fallot repair: a multicenter study", I designed the study, drafted the protocol, recruited participating centers, collected data, created a database, performed data analysis, reviewed the literature, composed the article, responded to comments from editors and reviewers, submitted the final manuscript, presented the data at an international symposium, and received the "Outstanding Research Award in Pediatric Cardiology" from the American Heart Association in November 2003.

The second and senior authors, Michael Landzberg and Edward Walsh, supervised the project, contributed to the intellectual content of the discussion, and corrected the first and final drafts of the manuscript. Michael Gatzoulis contributed one third of recruited patients, oversaw data collection from six centers that had previously participated in a cohort study under his direction, and corrected the first and final drafts of the manuscript. Hugues Lucron and François Marçon contributed another one third of patients to the study and corrected first and final drafts of the manuscript. As thesis supervisor, Jean Lambert oversaw all aspects of protocol design and analysis and corrected all versions of the manuscript. Mark Alexander supervised data collection on patients from Harvard University and corrected the first and final drafts.

As first author of the manuscript entitled, "Long-term outcomes after atrial switch for transposition of the great arteries: a meta-analysis comparing Mustard and Senning procedures", I designed the meta-analysis, performed an extensive literature search, contacted authors for primary patient data, extracted data from relevant articles, performed data analysis, completed the systematic review, responded to comments from editors and reviewers, submitted the final article, and presented the data. Michael Landzberg provided expertise in adult congenital heart disease, contributed to the intellectual content of the discussion, and corrected the first and final drafts of the manuscript. Jean Lambert supervised all aspects of study design and data analysis and corrected all versions of the manuscript. Clare O'Donnell contributed to designing the study, contacting authors for primary patient data, extracting data, error checks, and correcting the first and final drafts of the manuscript.

As first author of the manuscript entitled, "Lower incidence of thrombus formation with cryoenergy versus radiofrequency catheter ablation", I completed an extensive literature search, performed all aspects of data analysis, composed the article, responded to comments from editors and reviewers, submitted the final manuscript, presented the data, and contributed to an FDA presentation leading to approval of the technology for clinical use in the United States. As senior author, Marc Dubuc supervised this endeavor, oversaw the animal laboratory, performed catheter ablation, contributed to the intellectual content of the discussion, and corrected all versions of the manuscript. Patrick Chauvet and John Lehmann were implicated in protocol design and preliminary analyses, composed portions of the methodology section, and corrected the first and final drafts of the manuscript. Jean Lambert oversaw all aspects of data analysis and corrected all versions of the manuscript. Laurent Macle performed a substantial proportion of catheter ablations. Jean-François Tanguay and Martin Sirois conducted all histological analyses and morphometric measurements. Domenic Santoianni contributed his expertise as an engineer for the technical aspects of cryocatheter design and settings.

Value of Programmed Ventricular Stimulation after Tetralogy of Fallot Repair: a Multicenter Study

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Abstract

Background—Studies have consistently shown that ventricular tachycardia (VT) and sudden cardiac death (SCD) complicate the long-term outcome following tetralogy of Fallot repair, yet the diagnostic and predictive value of electrophysiologic testing in this population is uncertain.

Methods and Results—A multicenter cohort of 252 patients with repaired tetralogy of Fallot undergoing programmed ventricular stimulation was followed for 18.5±9.6 and 6.5±4.5 years after corrective surgery and electrophysiologic testing, respectively. Clinical VT and/or SCD occurred in 24.6%. Sustained monomorphic and polymorphic VT were induced in 30.2% and 4.4%. Including polymorphic VT in the definition of inducibility improved sensitivity (66.1±6.0% versus 77.4±5.3%, P=0.0082) with a marginal reduction in specificity (81.6±2.8% versus 79.5±2.9%, P=0.0455). Positive and negative predictive values were 55.2±5.3% and 91.5±2.2%. Independent risk factors for inducibility were age at study ≥18 years (OR 3.3), palpitations (OR 2.8), prior palliative surgery (OR 3.1), modified Lown's criteria ≥2 (OR 5.6), and cardiothoracic ratio ≥0.6 (OR 3.3). Event-free survival rates in non-inducible and inducible patients at 1, 5, 10, and 15 years were 97.9%, 92.8%, 89.3%, 89.3% versus 79.4%, 62.6%, 58.7%, and 50.3%, respectively (P<0.0001). Both inducible monomorphic (RR 5.0, P=0.0002) and polymorphic (RR 12.9, P<0.0001) VT predicted future clinical VT and SCD. In a multivariate analysis, inducible sustained VT was an independent risk factor for subsequent events [RR 4.7, 95% CI (1.2,18.5), P=0.0268].

Conclusions—Programmed ventricular stimulation is of diagnostic and prognostic value in risk stratifying patients with repaired tetralogy of Fallot. In this patient population, inducible sustained polymorphic VT should not be disregarded as non-specific.

Key Words: tetralogy of Fallot, electrical stimulation, sudden death, arrhythmia

Condensed Abstract

Programmed ventricular stimulation was performed in 252 patients with surgically corrected tetralogy of Fallot followed for 18.5±9.6 years. Clinical ventricular tachycardia (VT) and/or sudden cardiac death (SCD) occurred in 24.6%. Adding sustained polymorphic VT to the definition of inducibility enhanced the diagnostic yield, with sensitivity 77.4% and specificity 79.5%. Event-free survival in non-inducible versus inducible patients at 1, 5, 10, and 15 years was 97.9%, 92.8%, 89.3%, 89.3% versus 79.4%, 62.6%, 58.7%, and 50.3%. Inducible sustained VT independently predicted subsequent clinical VT and SCD (RR 4.7). Programmed ventricular stimulation is of diagnostic and prognostic value in repaired tetralogy of Fallot.

Tetralogy of Fallot is the most common cyanotic heart disease beyond infancy, accounting for 10% of all congenital heart malformations.[1] "Corrective" intracardiac repair has been performed for over 40 years with excellent results.[2,3] Nevertheless, ventricular arrhythmias have consistently been reported, and sudden cardiac death (SCD) is the most common cause of mortality late after repair.[4-6] Considerable efforts have been directed towards identifying predictors to stratify patients into high and low-risk categories for these events. Programmed ventricular stimulation has been used in selected patients at many centers, however, attempts to clarify its predictive value have been limited by small patient numbers and relatively low event rates.[7-9] We sought to assess the diagnostic value and prognostic significance of programmed ventricular stimulation in a multicenter cohort with repaired tetralogy of Fallot.

Materials and Methods

Study Population

The cohort consisted of patients with repaired tetralogy of Fallot and programmed ventricular stimulation performed between 1985 and 2002 from Children's Hospital Boston, Centre Hospitalier et Universitaire de Nancy, and six centers that recently identified noninvasive risk factors for tetralogy of Fallot[5] (Royal Brompton Hospital, Children's Hospital of Pittsburgh, The University of Minnesota Hospital and Clinic/Variety Club Children's Hospital, South Carolina Children's Heart Center, Tokyo Women's Medical College, and the Toronto Hospital). Patients with unrepaired tetralogy, pulmonary atresia, atrioventricular canal, and double-outlet right ventricle were excluded. Aspects of subsets of these populations have previously been reported.[5,8,10]

Data Collection and Follow-up

Data were collected in accordance with individual hospital institutional review board policies. Details regarding baseline characteristics, surgical history, symptoms prior to electrophysiologic testing, hemodynamic parameters, electrocardiographic measures, Holter recordings, cardiothoracic ratios, sustained atrial arrhythmias, antiarrhythmic agents, pacemakers, implantable cardioverter-defibrillators (ICD), and deaths were obtained. Sources included electronic and paper cardiologic, surgical, electrophysiologic, echocardiographic, hemodynamic, radiographic, and electrocardiographic charts and databases supplemented by records from referring physicians. Characteristics at the time of programmed ventricular stimulation or the most recent studies within one year prior to testing were recorded and analyzed.

Electrocardiographic parameters including QRS axis and maximum duration were measured manually from standard 12-lead electrocardiograms (25 mm/s and 1 mV/cm) in sinus rhythm and off antiarrhythmic agents.[11] Cardiothoracic ratios were calculated using posterioanterior chest radiographs.[12] Data from M-mode, two-dimensional, and Doppler echocardiography, cardiac catheterization, and cardiac magnetic resonance imaging (MRI) were recorded with particular attention to right ventricular pressures and severity of tricuspid and pulmonary regurgitation (graded absent, mild, moderate, or severe). Ventricular ectopy from standard Holter monitors were classified according to modified Lown criteria.[13]

The primary end-point was a composite of sustained ventricular tachycardia (VT) or SCD, whether or not resuscitation was successful. VT was considered sustained if it persisted ≥30 seconds or required electrical conversion. SCD was defined as death attributed to a cardiac cause occurring within one hour of acute symptoms.[14] To assess the prognostic significance of programmed ventricular stimulation, time zero was defined as time of electrophysiologic testing and patient-years were accrued until occurrence of the primary outcome, study termination, or death from other causes.

Programmed Ventricular Stimulation

Electrophysiologic studies were performed under conscious sedation in a drug-free state. Programmed ventricular stimulation was achieved at twice diastolic threshold at two or more right ventricular sites (typically apex and outflow tract) with at least two eight-beat drive trains (cycle lengths between 400 and 600 msec) and up to three extrastimuli with coupling intervals no less than 180 msec. In the absence of inducible VT, the protocol was repeated in all but five patients with an isoproterenol infusion titrated to increase heart rate by 20 to 50%. Ventricular burst pacing and S5 protocols were not routinely employed. Results were classified into three categories: negative, sustained monomorphic VT, and sustained polymorphic VT. Sustained VT was defined as persisting ≥30 seconds or requiring cardioversion. Induction of non-sustained VT was not coded consistently by all contributing centers and could not be analyzed in this study. If more than one study was performed, results from the earliest were retained for analysis.

Standard definitions were used for sensitivity, specificity, diagnostic accuracy, and predictive values of programmed ventricular stimulation in identifying patients with clinical sustained VT or SCD. Positive [LR(+)] and negative [LR(-)] likelihood ratios were defined as sensitivity/(1-specificity) and (1-sensitivity)/specificity, respectively.[15]

Statistical Analysis

Continuous variables are presented as means±standard deviations and dichotomous variables as percentages. Baseline characteristics and clinical outcomes according to results of programmed ventricular stimulation were compared using chi-square, Fisher's exact, one-way ANOVA, or McNemar's tests where appropriate. Logistic regression models were used to identify predictors of inducible VT. Event-free survival curves were plotted and compared using the Kaplan-Meier method and log-rank statistic.[16] To assess the predictive value of inducible VT, multivariate Cox proportional hazard models[17] accounted for duration of follow-up and adjusted for clinical, surgical, hemodynamic, electrocardiographic, and radiographic variables. The proportional-hazards assumption was verified by time-dependent interactions and goodness-of-fit statistics (weighted Schoenfeld residuals). Two-tailed P-values <0.05 were considered statistically significant. Testing was performed with SAS software Version 8 (SAS Institute, Cary, NC).

Results

Baseline Characteristics

A total of 252 patients, 59.4% male, with repaired tetralogy of Fallot underwent programmed ventricular stimulation at age 16.0±12.3 years (range 3.3 to 55.6 years). Follow-up duration after corrective surgery and programmed ventricular stimulation were 18.5±9.6 years and 6.5±4.5 years. Electrocardiograms were available in 100%; chest x-rays 97%; echocardiograms 97%; Holters 95%; cardiac catheterization 94%; and cardiac MRI 6%. Valvular regurgitation severity by MRI and echocardiography were concordant in all but one case where "probably mild" pulmonary regurgitation by echocardiography was graded moderate by MRI; the latter was retained.

Median age at corrective surgery was 4.5 years and 57.2% had transannular right ventricular outflow tract patches. Surgical palliation with systemic to pulmonary shunting was performed prior to repair in 46.3%. Age at repair and prior palliative shunt did not differ significantly by enrollment site. At the time of programmed ventricular stimulation, QRS duration was 146±36 msec, with QRS≥180 msec in 19.4% and left anterior hemiblock in 22.6%. Right ventricular systolic and end-diastolic pressures were 44±16 and 8±4 mmHg, with 74.2% and 14.3% having at least moderate pulmonary and tricuspid regurgitation, respectively. The average cardiothoracic ratio was 56.3±6.1%. Prior to electrophysiologic testing, 27.7% reported palpitations, 23.6% syncope, 16.7% had documented sustained VT, and 1.2% were resuscitated from cardiac arrest. Characteristics stratified according to results of programmed ventricular stimulation are summarized in Table 1.

Diagnostic Value of Programmed Ventricular Stimulation

Sustained monomorphic VT was induced in 30.2% (n=76), sustained polymorphic VT in 4.4% (n=11), and 65.5% (n=165) were non-inducible. An average of 2.7±0.6 extrastimuli were required for induction, with an isuprel infusion in 23.5%. Of initially negative studies, 11% became positive with isuprel. Of 87 patients with inducible sustained VT, 26 received antiarrhythmic therapy alone, 15 had ICDs alone, and 8 both antiarrhythmics and ICDs. VT ablation was performed in three patients at the initial study (and four others following recurrent events). The primary outcome occurred in 62 patients (24.6%): VT alone in 45, VT and SCD in 14, and SCD without documented VT in 3 patients. Three died of other causes: end-stage congestive heart failure, recreational drug overdose, and cerebral edema following right ventricular outflow tract revision. The latter patient had experienced clinical sustained VT prior to his demise.

Table 2 classifies patients according to two definitions of inducibility, depending on whether sustained polymorphic VT is considered positive. Diagnostic characteristics of programmed ventricular stimulation are summarized accordingly in Table 3. Including polymorphic VT resulted in greater sensitivity (77.4±5.3% versus 66.1±6.0%, P=0.0082) with a marginal decrease in specificity (P=0.0455). Overall diagnostic accuracy approached 80%. Greater than threefold increase in odds of clinical VT or SCD followed a positive study [LR(+) 3.77]. Compared to inducible monomorphic VT alone, a negative study was associated with a greater reduction in odds of the combined outcome [LR(-) 0.28 versus 0.42]. Predictors of inducible sustained monomorphic or polymorphic VT, odds ratios, and 95% confidence intervals are summarized in Table 4. Of note, presence of a left anterior hemiblock did not predict inducibility (P=0.6757).

Prognostic Significance of Programmed Ventricular Stimulation

Following programmed ventricular stimulation, 16.8% experienced sustained VT or SCD: VT alone 8.1%; SCD alone 3.7%; VT and SCD 5.0%. Actuarial event-free survival rates of the entire cohort at 1, 5, 10, and 15 years were 91.5%, 82.7%, 79.2%, and 74.3%, respectively (Figure 1A). Induction of sustained monomorphic (RR 5.0) and polymorphic (RR 12.9) VT were powerful predictors of subsequent events (Table 5 and Figure 1B). Event-free survival rates in non-inducible and inducible patients at 1, 5, 10, and 15 years were 97.9%, 92.8%, 89.3%, 89.3% versus 79.4%, 62.6%, 58.7%, and 50.3%, respectively ($P<0.0001$). Kaplan-Meier event-free survival curves are illustrated in Figure 2. Mode of VT induction, including number of required extrastimuli, was not predictive of subsequent events (P=0.9162).

Inducible sustained monomorphic or polymorphic VT remained an independent predictor of outcome [RR 4.7, 95% CI (1.2,18.5), P=0.0268] in multivariate regression analyses controlling for age at corrective surgery and electrophysiologic testing, gender, presence of a transannular patch, prior palliative surgery, clinical symptoms, QRS duration, right ventricular pressures, at least moderate tricuspid or pulmonary regurgitation, atrial arrhythmias, cardiothoracic ratio, class I or III antiarrhythmic agents, and presence of an ICD. Excluding the 29 patients with ICDs and three with primary VT ablation (two also had ICDs), positive programmed ventricular stimulation remained a powerful predictor of clinical VT and SCD [RR 4.9, 95% CI (1.9,12.6), P=0.0012].

Routine Screening versus Clinical Indication for Programmed Ventricular Stimulation

Overall, 93 patients (36.9%) had programmed ventricular stimulation as "routine" screening whereas 159 (63.1%) had clinical symptoms and/or recorded ventricular arrhythmias that prompted further testing. Test characteristics in these patient subgroups are summarized in Table 6. Inducible sustained monomorphic or polymorphic VT independently predicted subsequent clinical VT or SCD in patients routinely screened [RR 10.4, 95% CI (1.1, 100.2), P=0.0425] and with clinical indications [RR 4.2, 95% CI (1.6, 11.2), P=0.0036] for programmed ventricular stimulation.

Discussion

Despite encouraging results with surgical repair of tetralogy of Fallot,[2,3] late cardiac mortality due to ventricular arrhythmias and sudden death is observed in a substantial proportion of patients.[4-6;18;19] After the first 5-10 years following repair, a small but steady decline in freedom from VT and SCD has been observed, with 11.9% experiencing VT and 8.3% dying suddenly by 35 years.[5] Given that over 60% of patients in the present study had clinical indications prompting electrophysiologic testing, this cohort represents a higher-risk population, consistent with the 23.4% incidence of VT and 6.7% incidence of SCD over 18.5±9.6 years.

Considerable progress has been made towards identifying noninvasive risk factors for VT and SCD in corrected tetralogy of Fallot. In the largest cohort study to date,[5] independent predictors of clinical VT were QRS ≥180 msec and annual increase in QRS duration. Additional risk factors for SCD have included older age at repair, presence of a transannular right ventricular outflow tract patch, frequent ectopic beats,[20;21] increased right ventricular systolic pressures,[19,22;23] complete heart block,[19,24] and increased JT dispersion.[25,26] Despite advances in noninvasive risk stratification, identification of high-risk subgroups has not been sufficiently accurate to reliably guide management decisions. Attempts to clarify the utility of electrophysiologic testing had previously been limited by small numbers of adequately studied patients and relative infrequent occurrence of subsequent events, precluding meaningful estimates of diagnostic and predictive values.[7-9]

In this patient population, the 34.5% rate of inducible sustained VT was similar to 34.8% reported in post infarction patients with ejection fractions ≤40% and nonsustained VT.[27] Moreover, the diagnostic value [sensitivity 77.4%, specificity 79.5%, diagnostic accuracy 79.0%, LR(+) 3.77, and LR(-) 0.28] and prognostic significance (RR 4.7 for subsequent clinical VT or SCD), compared favorably to programmed ventricular stimulation post myocardial infarction.[28-30] Although several risk factors for inducible VT were identified, electrophysiologic testing independently predicted future events after controlling for these and other clinical, electrocardiographic, and hemodynamic variables. While the study was not designed to appraise therapeutic strategies, inducible sustained VT was a significant predictor of events in patients with and without antiarrhythmic agents, VT ablation, and ICDs.

The arrhythmic substrate in tetralogy has been likened to post infarction scar-related VT. Induced VT is most commonly monomorphic and macroreentrant, rotating clockwise or counterclockwise around myotomy scars or surgical patches.[20,31,32] In patients with coronary artery disease, inducible sustained polymorphic VT is considered either nonspecific or evidence of ventricular instability.[33,34] Antiarrhythmic therapy may convert inducible polymorphic VT into a more stable substrate.[35] Recent clinical trials have included sustained polymorphic VT in the definition of inducibility.[27,36] Interestingly, in this tetralogy of Fallot population, induction of sustained polymorphic VT was a powerful predictor of future events (RR 12.9) and its inclusion enhanced the diagnostic yield of programmed ventricular stimulation. Direct comparisons between inducible monomorphic and polymorphic VT should be interpreted with caution given the small number of patients with the latter arrhythmia. Nevertheless, inducible polymorphic VT post tetralogy repair should not be disregarded as nonspecific. Although not assessed in the current study, inducible non-sustained VT has also been associated with decreased survival in a mixed cohort of congenital heart patients.[10]

While the value of inducible VT as a risk factor post tetralogy of Fallot repair has been demonstrated, questions regarding patient selection for screening and the timing and frequency of testing remain to be elucidated. Test sensitivity, specificity, and likelihood ratios, increasingly considered the best available indices to evaluate diagnostic tests, are independent of prevalence assumptions.[15] Subgroup analyses have shown these parameters to be no different in patients "routinely screened" compared to those with clinical indications for testing. However, positive and negative predictive values are influenced by pre-test probability. Studies are currently assessing whether risk assessment based on non-invasive parameters may be helpful in pre-selecting patients for further testing with programmed ventricular stimulation. Finally, as risk increases with age and changes in underlying substrate may occur over time, careful follow-up is warranted.

Limitations

Given that selection criteria for electrophysiologic testing were not standardized, marginal distributions are not random and prevalence values reflect the heterogeneous patient population. While this may increase generalizability, prevalence estimates and positive and negative predictive values should be interpreted in this context. Unlike prognostic values, diagnostic test characteristics reflect a particular time-point (i.e. 18.5±9.6 years after corrective surgery) and may vary with duration of follow-up.

Medical and catheter-based therapeutic decisions were influenced by results of electrophysiologic testing and were not randomly allocated. However, direction of this potential bias is expected to result in underestimation of the predictive value of programmed ventricular stimulation as inducible patients are more likely to receive therapy directed towards reducing risk of VT and SCD. Analyses were performed with and without adjusting for antiarrhythmic therapy, but not β-blockers (insufficient data), and were repeated after excluding the few patients with primary VT ablation. Results were robust and essentially unaltered.

In contrast to other therapies, ICD implantation should theoretically not reduce incidence of the combined primary outcome as ICD therapy for sustained ventricular arrhythmias qualifies as an end-point. However, ICD implantation may result in a detection bias that overestimates the predictive ability of programmed ventricular stimulation, as patients with inducible VT are more likely to receive these devices that detect and record ventricular arrhythmias. Nonetheless, analyses performed in patients with and without ICDs yielded similar results (e.g. RR 4.7 versus 4.9).

Conclusions

In this multicenter cohort study, programmed ventricular stimulation was of diagnostic value and prognostic significance in risk-stratifying patients with repaired tetralogy of Fallot. Inducible sustained polymorphic VT enhanced the diagnostic yield and predictive ability and should not, therefore, be disregarded as a non-specific finding. Electrophysiologic testing predicted future clinical VT and SCD above and beyond known non-invasive risk factors. These results suggest that electrophysiologic testing may contribute importantly to risk-stratification algorithms designed to guide therapy to prevent clinical VT and SCD.

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Table 1. Patient characteristics

	No inducible VT N=165	Monomorphic VT N=76	Polymorphic VT N=11	Overall P-value
Age at electophysiologic study (years)	14.7±10.5	24.7±13.4	25.8±6.1	<0.0001
Male gender	61.0%	59.2%	36.4%	0.2764
Clinical presentation				
Palpitations	20.2%	40.0%	54.5%	0.0008
Syncope	13.4%	41.3%	54.5%	<0.0001
Atrial fibrillation/flutter	9.7%	17.1%	27.3%	0.0922
Documented sustained VT	4.2%	42.1%	27.3%	<0.0001
Cardiac arrest	0.6%	2.6%	0.0%	0.3795
Surgical history				
Age at corrective surgery (years)	5.4±5.6	7.7±5.8	7.2±6.6	0.0149
Transannular RV outflow patch	54.0%	61.8%	72.7%	0.2979
Prior palliative surgery	37.2%	67.6%	36.4%	<0.0001
Electrocardiogram				
QRS duration (msec)	135.3±32.6	164.7±33.4	169.1±26.9	<0.0001
QRS≥180 msec	8.5%	39.5%	45.5%	<0.0001
Left anterior hemiblock	21.8%	18.4%	63.6%	0.0031
Modified Lown ≥2 by Holter	28.7%	67.8%	40.0%	<0.0001
Hemodynamics				
RV systolic pressure (mmHg)	42.1±15.1	47.2±17.8	43.9±16.1	0.1299
RV end-diastolic pressure (mmHg)	8.1±3.8	8.9±4.0	8.8±3.6	0.3071
At least moderate PR	68.7%	87.8%	63.6%	0.0053
At least moderate TR	10.5%	23.0%	11.1%	0.0379
Cardiothoracic ratio (%)	55.3±5.7	58.8±6.5	55.1±5.7	0.0002
Follow-up				
Follow-up post surgical repair (yrs)	16.4±7.6	22.4±11.9	22.4±8.1	<0.0001
Follow-up post EP testing (years)	6.9±4.4	5.7±4.7	5.8±4.7	0.3199
Class I or III antiarrhythmic agent	12.1%	43.4%	9.1%	<0.0001
Pacemaker	11.4%	9.8%	0.0%	0.7070
ICD	3.6%	25.0%	36.4%	<0.0001
Clinical VT	3.8%	25.5%	60.0%	<0.0001
SCD	5.7%	11.8%	40.0%	0.0183

RV denotes right ventricle; PR, pulmonary regurgitation; TR, tricuspid regurgitation; EP, electrophysiologic

Table 2. Inducible VT and clinical VT or SCD

Results of programmed ventricular stimulation	Clinical VT or SCD		Total
	Yes	No	
Sustained monomorphic VT	41	35	76
No inducible monomorphic VT	21	155	176
Sustained monomorphic or polymorphic VT	48	39	87
No inducible sustained VT	14	151	165
Total	62	190	252

Table 3. Diagnostic value of programmed ventricular stimulation

	Sustained monomorphic VT	Sustained monomorphic or polymorphic VT	P-Value
Sensitivity	66.1±6.0%	77.4±5.3%	0.0082
Specificity	81.6±2.8%	79.5±2.9%	0.0455
Diagnostic accuracy	77.8±2.6%	79.0±2.6%	0.3657
Positive predictive value	53.9±5.7%	55.2±5.3%	N/A
Negative predictive value	88.1±2.4%	91.5±2.2%	N/A
Positive likelihood ratio	3.59	3.77	N/A
Negative likelihood ratio	0.42	0.28	N/A

N/A denotes not applicable

Table 4. Predictors of inducible sustained VT

Variable	Odds Ratio	95% Confidence Interval	P-Value
Univariate Analysis			
Age at EP study (years)	1.07	1.04,1.11	<0.0001
Age ≥18 years	6.0	3.0,12.3	<0.0001
Age at corrective surgery (years)	1.07	1.02,1.12	0.0060
Age ≥7 years	3.3	1.9,5.6	<0.0001
Palpitations	2.8	1.6,5.0	0.0004
Syncope	4.9	2.6,9.1	<0.0001
Prior palliative surgery	2.9	1.7,5.1	<0.0001
Documented AF/flutter	2.1	1.0,4.4	0.0522
QRS (msec)	1.03	1.02,1.04	<0.0001
QRS≥180 ms	7.3	3.6,14.6	<0.0001
Modified Lown ≥2	3.8	1.9,7.6	0.0002
RV systolic pressure (mmHg)	1.02	1.00,1.04	0.0574
At least moderate PR	2.5	1.3,5.0	0.0074
At least moderate TR	2.4	1.1,4.9	0.0201
Cardiothoracic ratio ≥0.60	3.3	1.8,6.1	0.0001
Multivariate Analysis			
Age at EP study ≥18 years	3.3	1.1,10.5	0.0416
Palpitations	2.8	1.2,6.8	0.0234
Prior palliative surgery	3.1	1.2,7.6	0.0163
Modified Lown ≥2	5.6	1.0,30.9	0.0493
Cardiothoracic ratio ≥0.60	3.3	1.2,8.8	0.0200

EP denotes electrophysiologic; AF, atrial flutter; RV, right ventricle; PR, pulmonary regurgitation; TR, tricuspid regurgitation

Table 5. Prognostic significance of inducible VT

EP testing	RR (95% CI)	P-Value	Actuarial freedom from VT and SCD			
			1 year	5 years	10 years	15 years
Negative	1.00	-	97.9%	92.8%	89.3%	89.3%
SMVT	5.0 (2.1,11.9)	0.0002	79.4%	67.1%	63.6%	63.6%
SPVT	12.9 (3.9,43.2)	<0.0001	80.0%	53.3%	26.7%	0.0%
SMVT or SPVT	5.8 (2.5,13.2)	<0.0001	79.4%	62.6%	58.7%	50.3%

EP denotes electrophysiologic; RR, relative risk; CI, confidence interval; SMVT, sustained monomorphic VT; SPVT, sustained polymorphic VT

Table 6. Programmed ventricular stimulation in routine screening versus clinical indication for testing

	Routine Screening N=93	Clinical Indication N=159	P-Value
Sensitivity	85.7±13.2%	76.4±5.7%	1.0000
Specificity	79.1±4.4%	79.8±3.9%	1.0000
Diagnostic accuracy	79.6±4.2%	78.9±3.2%	1.0000
Positive predictive value	25.0±8.8%	66.7±5.9%	0.0007
Negative predictive value	98.6±1.4%	86.4±3.5%	0.0084
Positive likelihood ratio	4.10	3.78	N/A
Negative likelihood ratio	0.18	0.30	N/A

N/A denotes not applicable

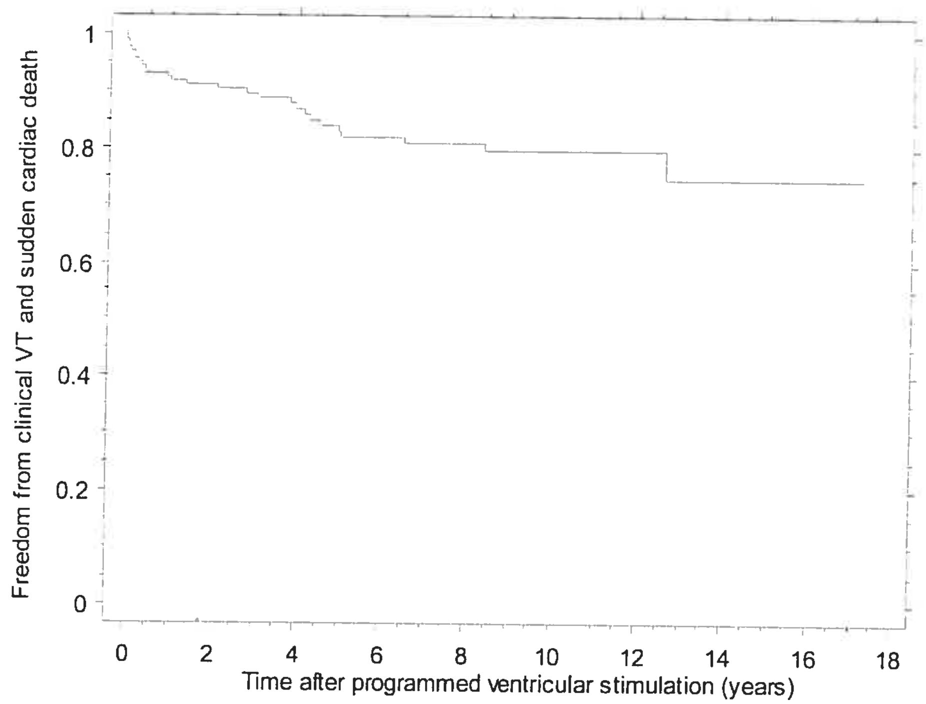
Legends

Figure 1. The Kaplan-Meier curve in Panel A plots survival free from clinical VT and SCD in the entire cohort. Panel B depicts event-free survival according to result of programmed ventricular stimulation.

Figure 2. Kaplan-Meier event-free survival curves are plotted and compared according to whether inducibility is limited to sustained monomorphic VT (Panel A) or includes sustained polymorphic VT (Panel B). Note the wider separation of curves when polymorphic VT is considered positive.

Figure 1. Freedom from clinical VT and sudden cardiac death in all patients and according to results of programmed ventricular stimulation

A



B

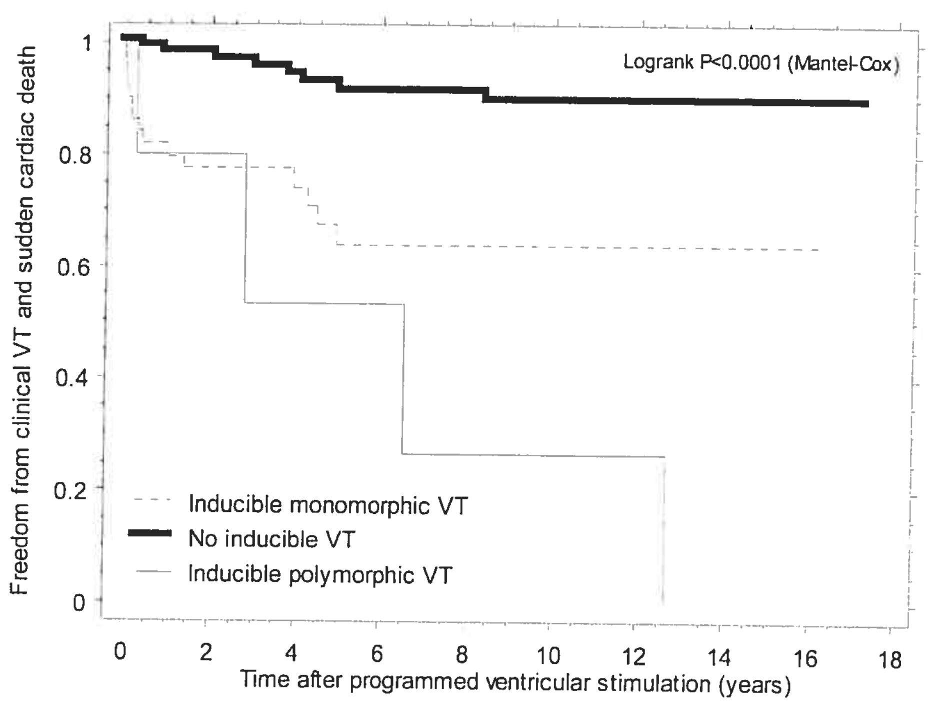
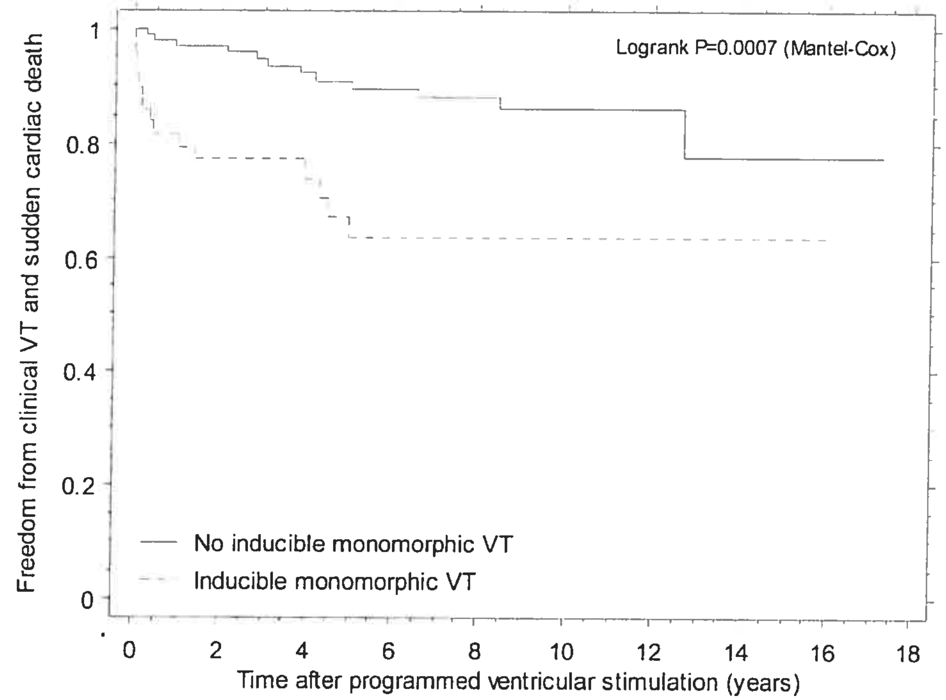
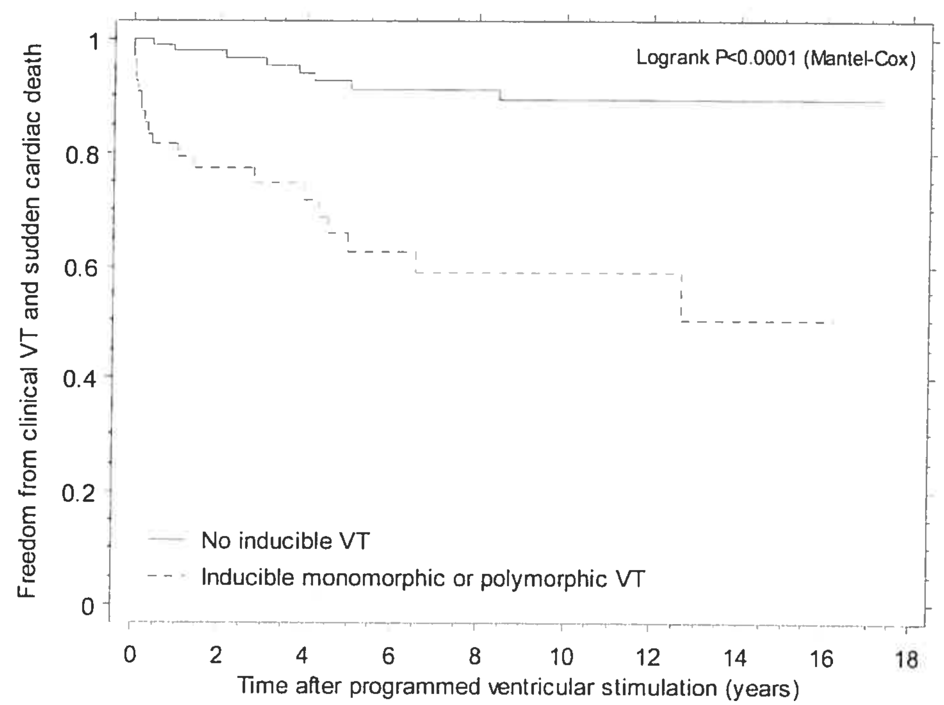


Figure 2. Freedom from clinical VT and sudden cardiac death according to whether or not polymorphic VT is included in the definition of inducibility

A



B



Long-term outcomes after the atrial switch for surgical correction of transposition: a meta-analysis comparing the Mustard and Senning procedures

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Running head: Mustard versus Senning repair for transposition

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Abstract

Most adults with regular transposition (the combinations of concordant atrioventricular and discordant ventriculo-arterial connections) have undergone either the Mustard or Senning procedure in childhood. It is unclear whether adverse events differ according to the surgery performed. With this in mind, we conducted a systematic review and meta-analysis to compare long-term outcomes. We searched systematically entries to MEDLINE and EMBASE databases from January 1966 through August 2003, supplementing the search by secondary sources. Comparative studies were required to include at least 10 patients in each cohort of Mustard or Senning procedure, and to report overall survival. Data were extracted by two independent reviewers. We used a components approach to assess quality. On the basis of assessment of heterogeneity, we then used a random-effects model for pooled analyses. In all, we included 7 studies, incorporating 885 patients. We found a trend towards lower mortality for the 369 patients undergoing a Mustard procedure when compared to 474 submitted to the Senning operation, with a hazard ratio of 0.63 and 95% confidence intervals between 0.35 and 1.14 (p=0.13). This increased with the size of the sample, giving an adjusted R^2 of 0.87 (p=0.004). Obstruction in the systemic venous pathway was more common in those having the Mustard procedure, with a risk ratio of 3.5 and 95% confidence intervals from 1.8 to 7.0 (p value less than 0.001), with a trend towards greater obstruction of the pulmonary venous pathway in those undergoing the Senning procedure, 7.6% versus 3.8% (p=0.27). A trend towards fewer residual shunts was observed for those with Mustard baffles, 7.0% versus 14.1% (p=0.10). Sinus nodal dysfunction, however, was more common after the Mustard procedure. Data regarding

atrial tachyarrhythmias was inconclusive. Systemic cardiac failure, and functional capacity, was similar. We conclude that outcomes are not uniform among patients submitted to the Mustard and Senning procedures. Knowledge of such differences may facilitate stratification of risk, and follow-up.

Introduction

Regular transposition, the segmental combination of concordant atrioventricular and discordant ventriculo-arterial connections, accounts between 5% and 7% of all congenital cardiac malformations.[1] Untreated, nine of ten infants born with the condition die within the first year of life.[2] In 1959, Senning introduced the operation in which insertion of an intraatrial baffle redirected the systemic and pulmonary venous returns without the use of grafts or prostheses.[3] In 1964, Mustard described an alternate technique for redirecting the venous pathways using an intraatrial pericardial patch.[4] Although the arterial switch[5] has now supplanted atrial redirection as the procedure of choice in many centres, the large majority of adults with transposition have had intraatrial repairs. Late complications have included sinus nodal dysfunction, atrial tachyarrhythmias, leaks across the baffle, obstruction to either the systemic or pulmonary venous pathways, or both, systemic right ventricular dysfunction, and sudden cardiac death.[6-12] Reports have yielded conflicting results as to whether the type of atrial reconstruction is associated with different risks regarding specific complications and overall survival. To characterize relative benefits, and compare the complications of each approach, we performed a systematic review and meta-analysis comparing outcomes over the long term for the two procedures.

Materials and methods

Literature search and selection of studies

We made electronic searches of MEDLINE and EMBASE databases, covering the period from January 1966 through August 2003, using the following query terms:

Senning, *Mustard*, *atrial switch*, or *atrial baffle* combined with *transposition*. The search was not limited to a particular language of publication. This strategy was supplemented by manual retrieval of secondary sources, including references from primary articles, and chapters from textbooks covering congenital cardiac malformations.

In the absence of randomized trials, we sought comparative observational peer-reviewed studies. Given that the primary objective was to compare overall survival in patients who had undergone either the Mustard or Senning procedures for correction of transposition, we mandated the following criterions for inclusion:

- follow-up reported for patients submitted to both procedures
- a minimum of 10 patients per exposure category
- provision of overall rates of survival, or sufficient data included to permit calculation of accurate estimates.

We excluded case series limited to one surgical approach, review articles, letters, editorials, and case reports. To avoid duplication, we reviewed multiple publications from the same centre(s) that met the above criterions. The manuscript reporting the greatest number of patients was retained, and smaller studies excluded. Data relating to individual patients was requested from the authors of all eligible studies.

Extraction of data and assessment of quality

Two independent reviewers extracted data from tables, text, and figures. Discrepancies were subject to checks for error, and adjudicated by discussion amongst our group. Consensus was obtained for all variables. Prespecified baseline data elements for each trial included year of publication, age at surgery, gender, weight, duration of follow-up, total number of patients, subdivisions by type of surgery, that is Mustard or Senning, and the complexity of the underlying lesion, including the association with deficient ventricular septation. Measures of outcome were overall survival, obstructions and leaks related to the baffle, atrial brady- and tachyarrhythmias, systemic ventricular failure, and functional capacity. The quality of the studies was assessed on the basis of criterions that included its design, that is retrospective or prospective, the size of the sample, the number of participating centres, whether criterions for inclusion and exclusion were detailed, accountability for losses to follow-up, and whether survival was further subclassified by presence or absence of a ventricular septal defect. Where the primary end-point was not explicitly presented as the ration of the log hazard ratio and its variance, estimates of these statistics were extracted from survival curves[13,14] or indirectly calculated[15-17] using the methods described by Parmar and colleagues.[18]

Statistical analysis

The calculated combined statistic for the primary measure of outcome was a hazard ratio for time to event data with 95% confidence intervals. The decision to proceed with a random effects, rather than using a fixed effects model, was based on testing for variations between studies. A Q-statistic greater than k-1, or H value greater than 1, where $H^2=Q/(k-1)$, was considered to indicate substantial heterogeneity between the studies compared.[19] The random effects model, as described by DerSimonian and Laird,[20] incorporated heterogeneity between and within studies into calculations of the common effect, and used precision weighting by the method of inverse variance.

Given the nature of non-randomized and non-blinded observational studies, we did not use a formal composite scale for assessment of quality. Instead, we favoured a "component approach", where the importance of individual domains of quality, and the direction of potential biases associated with these domains, were examined in meta-regression analyses that modeled the logarithm of the hazard ratio as the dependent variable.[21] Potential publication bias was assessed by plotting standardized effect versus precision, using Egger's publication bias plot, and Begg's funnel plot of the logarithm of the hazard ratio and its standard error. Secondary categorical end-points reported in less than five studies were combined with weights based on the size of the samples and compared with chi-square tests. Statistical analyses were performed using Stata version 7.0 (Stata corporation, College Station, Texas), and SAS software Version 8 (SAS Institute, Cary, North Carolina).

Results

Selection of studies

The electronic search yielded a total of 265 articles (Fig. 1). We identified 3 additional potentially relevant studies through searching secondary sources and textbooks related to congenital cardiac malformations. Of these studies, 11 met the screening criterions. The 257 articles excluded were essentially review articles, case series restricted to only one surgical approach, case reports, editorials, or letters. From the 11 remaining studies, two were excluded to avoid duplication of results originating from the same centre.[22,23] One study described outcomes in 89 patients undergoing atrial redirection procedures without further subdividing the results by the Mustard and Senning operations.[24] An additional study described arrhythmias in 17 and 15 patients after the Mustard and Senning procedures, respectively, but did not include data relating to survival.[25] We made contact with the authors from both these manuscripts, but their primary databases were not available. The meta-analysis was conducted on the seven remaining studies, and included a total of 885 patients.[13-17,26,27]

Populations studied

All studies were non-randomized, and included consecutive patients with transposition undergoing atrial repair within a defined time frame. One study was multicentric, involving 20 sites,[26] and two were prospective in design.[13,26] In 2 studies, the population studied had been identified by age at time of surgery. This was less than 15 days in one,[26] and less than 100 days in the other.[17] We excluded 2 studies based on patients with complex transposition, defined as having one or more associated ventricular septal defects.[14,16] Other exclusion criterions were associated atrioventricular valvar abnormalities and coarctation,[14] and associated anomalies other than ventricular septal defect, such as pulmonary stenosis, persistent patency of the arterial duct, and atrial defects within the oval fossa.[27] One study mandated a minimum duration of follow-up of 18 months.[17] The characteristics summarized are shown in Table 1.

Overall survival

Overall postoperative hospital mortality ranged from 3.1% to 10.0%. For the combined population undergoing atrial redirection, actuarial survival at 8 to 16 years ranged from 78% to 84%. Reported risk factors for death included younger age and lower birth weight at repair,[26] female gender,[26] presence of a ventricular septal defect,[26,27] cardiac positional anomalies,[26] active arrhythmias,[27] surgery involving the left ventricular outflow tract,[26] and prior banding of the pulmonary trunk.[26] Causes of death were not uniformly detailed, but included sudden cardiac death,[13,14,26,27] cardiac failure,[13-16,26,27] baffle obstruction,[14,26] and perioperative death following surgical revision.[13,14,26]

Hazard ratios from individual studies comparing overall survival following the Mustard versus the Senning procedures are depicted in Table 2. In the study by Mahony et al.,[17] no deaths were reported over a median follow-up of 2.7 years, thereby precluding calculation of an estimate of risk. A forest plot, pooling the remaining six studies, and including 369 patients undergoing the Mustard procedure, and 474 having the Senning procedure, is shown in Figure 2. As testing for heterogeneity was considered positive, the Q statistic being 7.431, with 5 degrees of freedom (p=0.191, H=1.219), we pursued a random effects model. We discovered a trend towards lower overall mortality after the Mustard compared to the Senning procedure, with a hazard ratio of 0.63 and 95% confidence intervals between 0.35 and 1.14 (p=0.13). Hazard ratios from individual studies ranged from 0.29, with 95% confidence intervals between 0.15 and 0.58, in the multicentric prospective cohort, which provided the most precise estimate, to 5.00, with 95% confidence intervals between 0.06 and 388.6, in the study with the smallest sample.

Analysis of individual components of quality detected no differences in outcome as judged on the basis of mortality outcome for the following candidate variables:

- prospective versus retrospective study design (p=0.34),

- both surgical approaches performed concurrently versus adjacent time periods (p=0.34),
- fully detailed inclusion and exclusion criteria (p=0.57),
- and accountability for losses to follow-up (p=0.57).

Moreover, the proportion of patients undergoing the Mustard (p=0.42) and Senning (p=0.25) procedures for complex forms of transposition, and the ratio of the two (p=0.92), did not influence outcome.

The effect of the size of the sample on outcome, however, did account for a significant proportion of the heterogeneity between studies, with an adjusted R^2 of 0.87 (p=0.004). The larger the sample, the greater the relative benefit of the Mustard as opposed to the Senning procedure on total mortality (Fig. 3). The influence of size of the sample on outcome was further explored by assessing potential bias between publications. A graphical funnel plot in Figure 4 demonstrates asymmetrical results around the pooled estimate. The absence of studies with larger standard errors, in other words less precision, favouring the Mustard procedure suggests potential publication bias, resulting in underestimation of the relative benefit of the Mustard procedure on mortality.

Obstructions and residual shunts related to the baffle

Means of assessing, classifying, and reporting leaks and obstructions related to the baffle varied widely among studies. The most common site of obstruction was consistently reported to be the superior limb of the systemic venous pathway.[14,16,17,26] Obstruction of the systemic venous pathway (Table 3) was present in 35.6% of a combined 211 patients from 4 studies when defined as a gradient by cardiac catheterization at least 3 millimetres of mercury,[14] or 5 millimetres of mercury,[16,17,27] with a uniformly higher incidence in patients undergoing the Mustard procedure, the hazard ratio being 3.5, with 95% confidence intervals between 1.8 and 7.0 (p value less than 0.001). In contrast, pulmonary venous obstruction, defined as a haemodynamic gradient by cardiac catheterization of at least 5 millimetres of mercury,[14,16] 10 millimetres of mercury,[17] or unspecified,[27] occurred in 11 of 211 combined patients, with a trend towards a lower incidence for those having the Mustard procedure, specifically 3.8% versus 7.6% (p=0.27).

A qualitative synthesis, and analysis of trends for the populations, revealed a predominantly higher risk for reintervention because of obstruction in the venous pathways in the early months following the initial procedure. Despite the high incidence of significant gradients across the baffle as defined above, the majority of patients was asymptomatic, and did not require surgical revision. Of a total of 554 patients from five studies that reported rates of reintervention,[14,16,17,26,27] 4.3% and 2.5% required revisions of the baffle because of obstruction in the systemic and pulmonary venous pathways, respectively. A greater proportion of patients undergoing the Mustard as opposed to the Senning procedure needed reintervention for systemic (9.7% versus 3.0%, p=0.045) but not pulmonary (p=0.98) venous obstruction. The perioperative mortality was considerable, with 7 of 24 (29%), and 3 of 14 (21%) patients dying after reinterventions to deal with obstructions in the systemic and pulmonary venous pathways.

Data on residual shunts was reported in four studies.[14,17,26,27] The definitions were either not provided,[26] determined by unspecified catheterization criterions,[17,27] or defined as a step-up of 8% measured with oximetry, or a shunt fraction 1.5 or greater for systemic to pulmonary shunts, and saturations of oxygen lower than 90% in the absence of pulmonary disease for pulmonary to systemic shunts.[14] In the two studies[14,27] that reported leaks across the baffle separately for 113 patients undergoing the Mustard procedure, and 85 having a Senning operation, we found a trend towards fewer residual shunts after the Mustard option, 7.0% versus 14.1% (p=0.10). In the entire cohort of patients, only six[17,26] required surgical revision because of a leak across the baffle, with no perioperative mortality.

Bradyarrhythmias

Substantial heterogeneity was noted with regards to definition of sinus nodal dysfunction, methods used for diagnosis, and reported frequency. Helbing et al.[27] cited the Kugler criterions[28] to define sinus nodal dysfunction, Bender et al.[16] averaged three corrected sinus nodal recovery times, and Deanfield et al.[13] defined intermittent and persistent junctional rhythm to be present if it accounted for between 10 and 50%, and greater than 50% of all heart beats, over a 24-hour period on serial Holter recordings. Qualitatively, the weight of evidence suggests potentially more sinus nodal dysfunction after the Mustard procedure. In an analysis reflecting survival, Helbing et al.[27] reported a significantly greater loss of sinus rhythm (p<0.001) for those having a Mustard as opposed to a Senning procedure, at 64.4% versus 32.6% at five years, and 82.2% versus 47.3% at 16 years of follow-up. Deanfield et al.[13] reported a similar trend, with loss of sinus rhythm in 35% of those having the Mustard procedure compared to 22% of patients having a Senning operation after five years of follow-up (p=0.09). Bender et al.[16] reported only one patient with sick sinus syndrome after the Senning operation. In one study,[14] 2 patients were reported to have died from bradyarrhythmias, specifically with sick sinus syndrome and atrioventricular block. In the 2 remaining studies, pacemakers were implanted in 2 of 52[17] patients, and 21 of 281[26] patients. The instantaneous risk for insertion of a pacemaker peaked at two to three years postoperatively, persisted until five years, and then gradually tapered.[26] Risk factors included complex associated malformations in those having a Senning procedure, and prior surgical atrial septectomy.

Atrial tachyarrhythmias

Only 2 of the 7 studies determined the presence of paroxysmal supraventricular tachycardias or atrial flutter by Holter monitoring and electrocardiographic follow-up.[13,27] Helbing et al.[27] reported paroxysmal atrial arrhythmias in 28.8% of those having the Mustard procedure, and 11.9% of patients after a Senning operation. The incidence of atrial arrhythmias found in the cohort of patients studied by Deanfield et al.[13] were 16.2% and 6.9% in patients undergoing the Mustard and Senning procedures, respectively. Actuarial rates, however, were not provided and, in both studies, the duration of follow-up was considerably longer in the patients who had undergone the Mustard as opposed to the Senning procedure, thereby obscuring analysis of comparative trends. Bender et al.[16] reported that 5.6% of their entire cohort had paroxysmal atrial arrhythmias, and 5.3% of patients in the multicentric study[26] had received antiarrhythmic agents.

Right ventricular (systemic) failure and functional capacity

Data on systemic right ventricular systolic function was available from 3 studies,[16,17,27] with equivalent results for the two procedures. By echocardiography, 21 of 60 patients had a moderately to severely depressed right ventricular (systemic) ejection fraction after the Mustard operation, in comparison to 23 of 62 patients undergoing the Senning procedure.[27] No significant differences were found after further subdividing patients into simple ($p=0.54$) and complex ($p=0.91$) transposition. Right ventricular ejection fractions as determined by cineangiography were similar prior to (46±2% versus 49±2%) and within one month postoperatively (39±5% versus 45±3%) for the two operations. Mahony et al.[17] reported that all their patients had enlarged right ventricles, with normal contractility by angiography.

The functional status of the patients was assessed in two studies at nine to 12 years,[26] and a mean of 13 years.[27] In both studies, over 95% of patients were in the first or second classes of the functional classification of the New York Heart Association. Pooling these 139 patients having the Mustard operation, and 135 submitted to the Senning procedure, the proportions in the first 3 functional classes were 64.0% versus 60.7%, 32.4% versus 34.8%, and 2.2% versus 3.0% ($p=0.81$). The predicted proportional maximum exercise tolerance was likewise equivalent in 24 patients after a Mustard procedure, and 14 after a Senning operation (82.5±15.1% versus 80.0±18.3%).[27] Marx et al.[14] reported two patients after a Senning procedure, but none after the Mustard operation, with severe systemic ventricular failure, and Helbing et al.[27] noted three deaths resulting from systemic heart failure after the Mustard, and two after a Senning procedure. These patients all had significant tricuspid regurgitation.

Signs of heart failure were first documented at four months, nine years, and 15 years following the initial surgery.

Discussion

Although rarely performed in the current era, the Mustard and Senning procedures revolutionized the care of patients with regular transposition.[3,4] As a result, the majority of patients born with this anomaly survived beyond infancy, indeed very often with good quality of life, to adulthood.[6,8,12] As more patients reached their adult years, however, the justified celebration of this success gave way to some dismay over the challenges posed by later morbidity and mortality. Medical caregivers face the daunting task of identifying patients at highest risk of developing late complications, with hopes to initiate preventive therapy directed towards evading adversity. Schemes for stratification of risk are sorely lacking, particularly with regards to differences between outcomes in patients who have had a Mustard as opposed to a Senning procedure.

The superiority of either surgical technique, and the relative risk of individual complications, have not been convincingly established. Proponents of the Senning procedure advance that minimal, if any, nonviable tissue or prosthetic material favors future growth and optimizes atrial function, with potential reduction in obstruction of the venous pathways and arrhythmias.[29-31] Supporters of the Mustard procedure have claimed lower mortality, reduction in systemic and pulmonary venous obstruction, and also suggest a decreased incidence of arrhythmias.[6,32-35] As evidence, the proponents have largely relied on data utilizing one or other technique, usually based on the experience from a single centre. This systematic review, and meta-analysis, assembles available data from studies that attempt to evaluate outcomes from the two techniques in comparable populations.

Our findings indicate a trend towards improved survival in those who have undergone the Mustard procedure, further reinforced by the stronger effect as the size of the sample increases and the possible publication bias. The cause of increased mortality in patients who have undergone the Senning operation merits further consideration. The most common cause of late mortality after an intraatrial redirection has consistently been reported to be sudden death.[6,8,36] Excess deaths observed after the Senning operation were unlikely bradyarrhythmic in nature, given that sinus nodal dysfunction occurred more frequently after the Mustard procedure. In light of inconclusive comparisons, a preponderance of late intraatrial reentrant tachycardias, and/or atrial fibrillation, cannot be excluded for those who have undergone the Senning procedure. Indeed, documented supraventricular tachycardia is a proposed risk factor for late mortality.[8,36] Although impaired systemic ventricular function in adults with transposition has been related to late clinical arrhythmias,[7] no differences in heart failure or functional class were identified in our study. Pulmonary vascular disease also accounts for a substantial proportion of deaths after atrial redirection,[8,37] and a trend towards more pulmonary venous obstruction was noted in those who had undergone the Senning procedure.

Limitations

Pooled analyses of observational studies that lack the experimental element of random allocation to a particular intervention present particular challenges as a result of inherent biases and differences in vigil of definitions, means of assessing outcome, and designs of the individual studies.[38] They may provide useful tools, nevertheless, to help understand and quantify sources of variability, summarize data, and generate hypotheses. The intention of our systematic review was to summarize the current state of knowledge, and derive the most precise assessment of effect, associated with the Mustard as opposed to the Senning procedures within the constraints of available non-controlled data. Each study was required to provide an individual estimate of effect or present sufficient data to calculate such. Studies presenting only one approach were excluded, as they inherently do not provide intra-study estimates necessary for the calculation of pooled outcomes in formal meta-analyses. To reduce the probability of producing precise but spurious results, the strategy of searching, and the criterions for inclusion, were deliberately broad, publications in all languages were considered, and potential sources of heterogeneity were carefully examined. Although actively sought, data from individual participants was not provided.

Several centres reported experience from a sequential use of one surgical technique and then the alternative. Interestingly, these shifts were not unidirectional. Procedures were adopted by surgeons in different centres in a complex pattern, with contributions from date of first report, the original centre of training of the surgeon, geographic location, influence of larger centres over smaller, publicity over early complications, technical difficulty, and increasing understanding of later complications. In addition, more complex factors may often be in play in these papers from an era of rapid expansion of a novel field. It is possible, for example, that centres experiencing difficulty with one procedure might alter their technique, and then be keen to report improved outcomes. In addition, other perioperative factors, including techniques of anesthaesia and postoperative care, were undergoing rapid evolution throughout the era of these reports.

Conclusion

Our results suggest a trend towards improved survival in patients with regular transposition who underwent a Mustard procedure. Patients undergoing the Mustard operation, nonetheless, appeared more likely to develop sinus nodal dysfunction, and obstruction within the systemic venous pathway, but were less likely to experience residual leaks across the baffle and obstruction of the pulmonary venous pathway. The perioperative mortality for patients undergoing revision of the baffle was considerable, emphasizing the importance of refinement of surgical and transcatheter therapeutic techniques. Follow-up data from multicentric studies may further refine the evaluation of long-term outcomes.

Acknowledgement

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Tables

Table 1. Overview of studies included in the meta-analysis

Variable	Wells WJ	Helbing WA	Deanfield J	Marx GR	Meisner H	Mahony L	Bender HW
Year published	2000	1994	1988	1983	1982	1982	1980
Year of surgery	1985-1989	1961-1987	1978-1982	1972-1980	1974-1981	1975-1981	1975-1979
Study design	Prospective	Retrospective	Prospective	Retrospective	Retrospective	Retrospective	Retrospective
No. of centers	20	1	1	1	1	1	1
No. patients	281	122	100	123	175	52	32
Mustard	108	60	46	66	73	36	16
Senning	173	62	54	57	102	16	16
Type of TGA							
Simple	246*	89	74	123	126	NA	32
Mustard	96*	46	30	66	64	NA	16
Senning	150	43	44	57	62	NA	16
Complex	35*	33	26	0	49	NA	0
Mustard	12*	14	16	0	38	NA	0
Senning	23	19	10	0	11	NA	0
Follow-up (mo.)						32.4	
Mustard	median>144	201/140†	~73/NA†	43.2±26.4	NA	NA	37±10
Senning	median>144	80.5/131†	~63/NA†	13.6±8.0	NA	NA	13±6
% Male							
Mustard	NA	62%	52%	92%	NA	NA	NA
Senning	NA	61%	59%	61%	NA	NA	NA
Age surgery (mo.)						1.7	
Mustard	<0.5	28.5/55.5†	10/8†	15.5±12.2	NA	<3.3	9.4±1.3
Senning	<0.5	8.0/11.0†	9/9†	6.6±5.0	NA	<3.3	4.8±0.9
Weight surg. (kg)						3.7	
Mustard	NA	NA	NA	NA	NA	NA	7.3±0.5
Senning	NA	NA	NA	NA	NA	NA	5.8±0.6

Abbreviations: mo. denotes months; NA, not available; No., number; TGA, concordant atrioventricular and discordant ventriculo-arterial connections

*Estimate based on figures presented prior to crossover of seven Mustard patients

†Subdivided into simple/complex transposition

Table 2. Hazard ratios for overall survival after the Mustard versus the Senning procedures from individual studies

	HR (95% CI)	p-value	Sample size	Weights
Wells et al.	0.29 (0.15, 0.58)	<0.001	281	8.275
Helbing et al.	0.86 (0.31, 2.38)	0.762	122	3.674
Deanfield et al.	1.32 (0.16, 11.07)	0.799	100	0.849
Marx et al.	1.67 (0.23, 12.21)	0.614	123	0.970
Meisner et al.	0.70 (0.34, 1.43)	0.324	175	7.575
Bender et al.	5.00 (0.06, 388.6)	0.144	32	0.203

HR denotes hazard ratio; CI, confidence interval

Table 3. Secondary outcomes after the Mustard as opposed to the Senning procedures

Secondary end-point	**Higher incidence**	**Comment**
Baffle obstruction		
Systemic venous pathway	Mustard	HR 3.5, 95% CI (1.8, 7.0), p<0.001
Pulmonary venous pathway	Senning	Trend: 3.8% versus 7.6%*, p=0.27
Residual shunt	Senning	Trend: 7.0% versus 14.1%*, p=0.10
Bradyarrhythmias	Mustard	e.g. loss of sinus rhythm at 5 years: 64% versus 33%*, p<0.001 [27] 35% versus 22%*, p=0.09 [13]
Atrial tachycardia	Inconclusive	Major differences in follow-up duration
Systemic heart failure		
RVEF	Equivalent	No differences in absolute or severely depressed RVEF [27]
NYHA functional status	Equivalent	I: 64% vs 61%*; II: 32% vs 35%*; III: 2.2% vs 3.0%*; p=0.81
Exercise tolerance	Equivalent	83% versus 80%* of maximal predicted functional capacity

HR denotes hazard ratio; CI, confidence interval; NYHA, New York Heart Association; RVEF, right ventricular ejection fraction

*Mustard versus Senning

Legends to Figures

Figure 1. Summary of the process for selection of articles

Figure 2. Overall survival in patients submitted to the Mustard as opposed to the Senning procedure

Figure 3. Effect of the size of the sample on the hazard ratio

Note the linear relationship between the size of the sample and the hazard ratio: as the size increases, a stronger effect is observed on overall mortality favoring the Mustard procedure.

Figure 4. Begg's funnel plot with pseudo 95% confidence intervals for potential bias in publication.

See text for discussion.

Figures

Figure 1. Summary of the the process for selection of articles

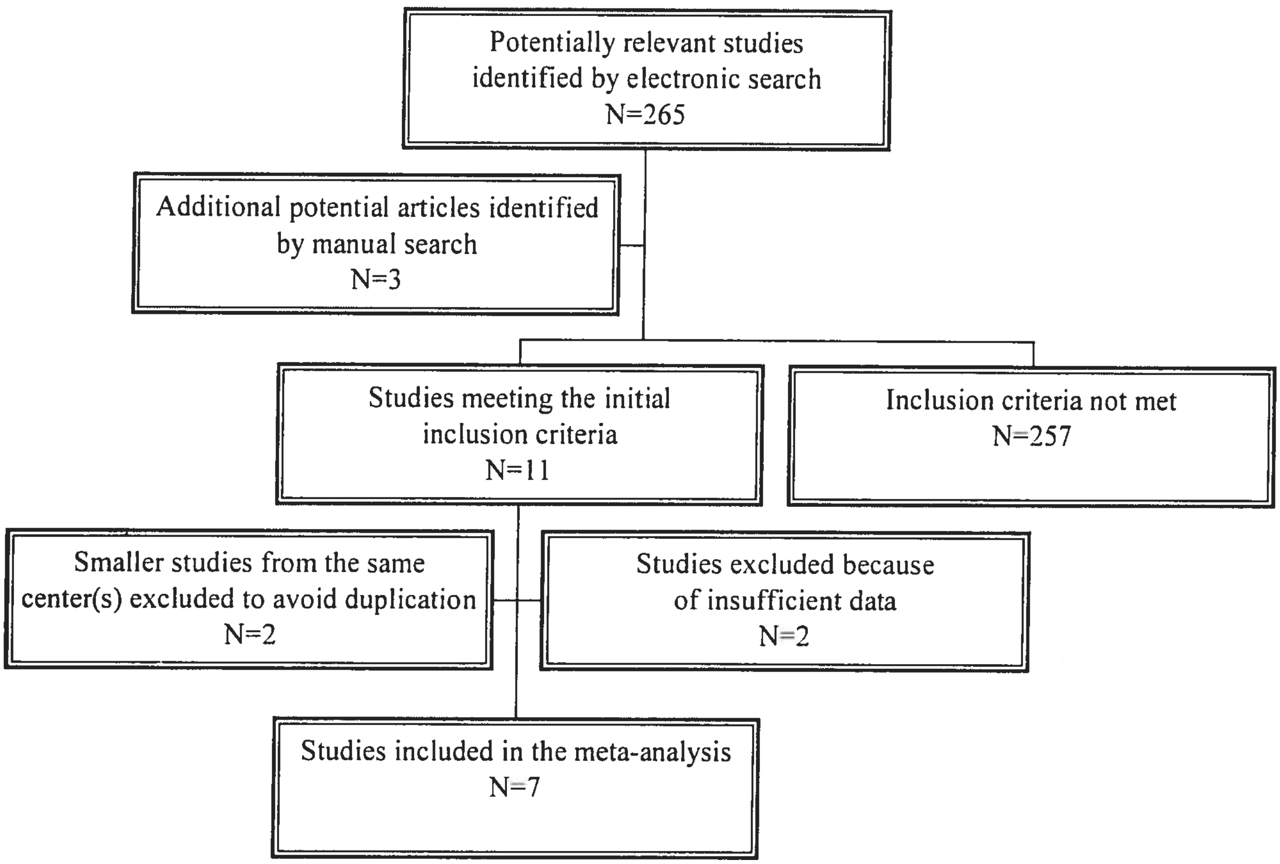


Figure 2. Overall survival in patients undergoing the Mustard as opposed to the Senning procedure

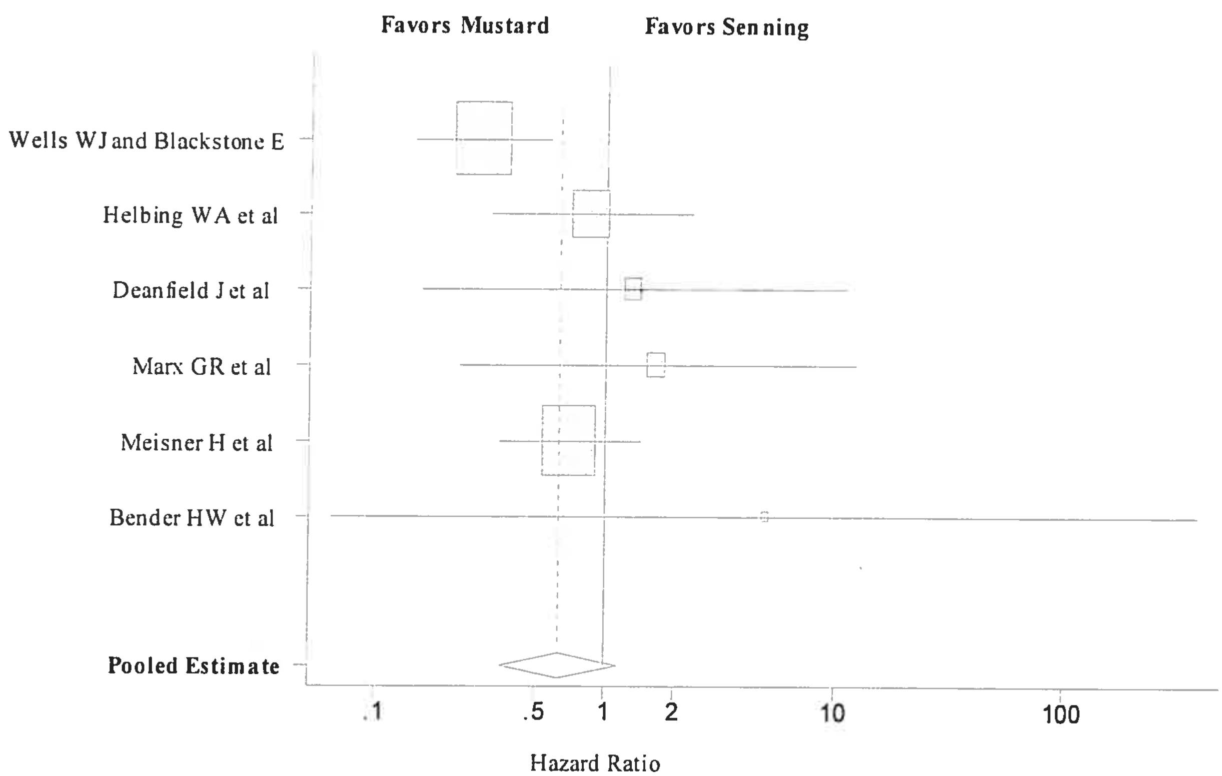


Figure 3. Effect of the size of the sample on the hazard ratio

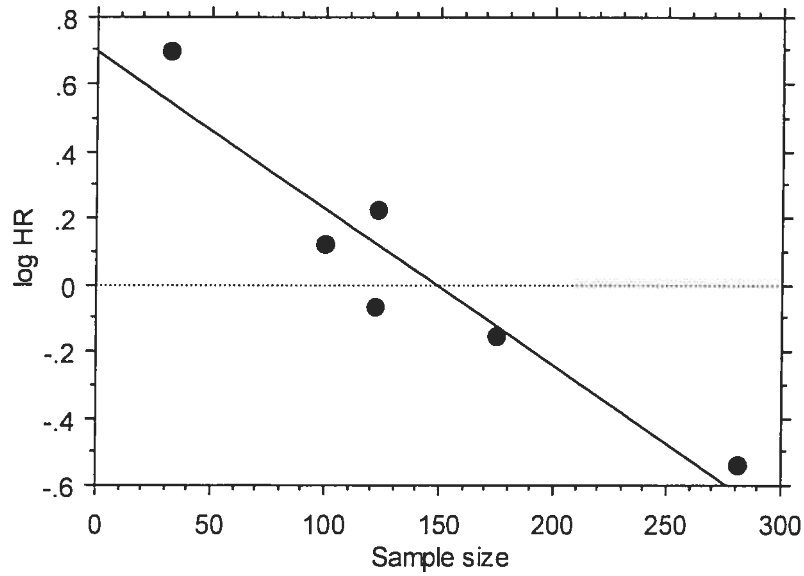
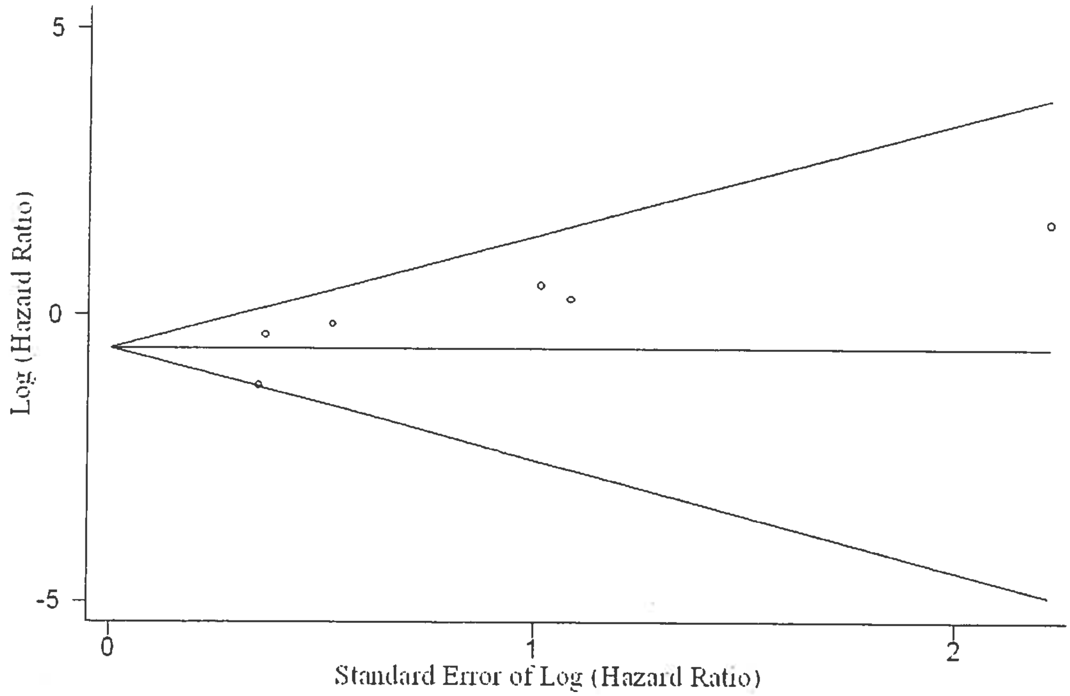


Figure 4. Begg's funnel plot with pseudo 95% confidence intervals for potential bias in publication



Lower Incidence of Thrombus Formation with Cryoenergy versus Radiofrequency Catheter Ablation

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[22] Ablation/ICK/surgery

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Abstract

Background—Radiofrequency (RF) catheter ablation is limited by thromboembolic complications. The objective of this study was to compare the incidence and characteristics of thrombi complicating RF and cryoenergy ablation, a novel technology for the catheter-based treatment of arrhythmias.

Methods and Results—Ablation lesions (n=197) were performed in 22 mongrel dogs at right atrial, right ventricular, and left ventricular sites preselected by a randomized factorial design devised to compare RF ablation with cryocatheter configurations of varying sizes (7-French and 9-French), cooling rates (-1°C/s, -5 °C/s, and -20 °C/s), and target temperatures (-55°C and -75 °C). Animals were pretreated with acetylsalicylic acid and received intraprocedural intravenous unfractionated heparin. Seven days following ablation, the incidence of thrombus formation was significantly higher with RF compared to cryoablation (75.8% versus 30.1%, P=0.0005). In a multiple regression model, RF energy remained an independent predictor of thrombus formation when compared to cryoenergy [OR 5.6, 95% CI (1.7, 18.1), P=0.0042]. Thrombus volume was also significantly greater with RF compared to cryoablation [median 2.8 mm^3 versus 0.0 mm^3, P<0.0001]. More voluminous thrombi were associated with larger RF lesions but cryolesion dimensions were not predictive of thrombus size.

Conclusions—RF energy is significantly more thrombogenic than cryoenergy, with a higher incidence of thrombus formation and larger thrombus volumes. Extent of hyperthermic tissue injury is positively correlated with thrombus bulk, whereas cryoenergy lesion size does not predict thrombus volume, likely reflecting intact tissue ultrastructure with endothelial cell preservation.

Condensed Abstract

Catheter ablation was performed in 22 dogs at atrial and ventricular sites preselected by a randomized factorial design devised to compare RF with cryolesions. After 7 days, the incidence of thrombus was significantly higher with RF (75.8% versus 30.1%, P=0.0005). In a multiple regression model, RF remained an independent predictor of thrombus formation (OR 5.6, P=0.0042). Thrombus volume was significantly greater with RF compared to cryoablation (2.8 mm^3 versus 0.0 mm^3, P<0.0001). More voluminous thrombi were associated with larger RF lesions but cryolesion dimensions were not predictive of thrombus size. In conclusion, RF energy is significantly more thrombogenic than cryoenergy.

Key Words: radiofrequency ablation; cryoablation; cryoenergy; thrombus; thromboemboli

Radiofrequency (RF) catheter ablation has become the treatment of choice for a wide variety of arrhythmias. Coagulation and tissue necrosis induced by hyperthermia is, however, associated with an inherent risk of thrombus formation. Clinically, a 0.6-0.8% incidence of thromboembolic events has been estimated.[1] This complication rate further increases when RF ablation is performed in systemic cardiac chambers (1.8% to 2.0%) and for ventricular tachyarrhythmias (2.8%). Moreover, use of intravenous heparin and temperature feedback to control RF current do not appear to eliminate thromboembolic risk.[1-3] More recently, percutaneous cryoenergy catheters have been used successfully in ablating atrioventricular nodes[4] and supraventricular tachycardias[5] in humans. The hypothermic tissue injury induced by this alternate ablation modality is thought to be non-thrombogenic.[6] Indeed, preliminary data suggest absence of histologically identifiable thrombus formation at the site of cryoenergy injury.[7] The objective of this study was, therefore, to prospectively compare incidence and characteristics of thrombi complicating RF and cryoenergy catheter ablation and identify predictors of the presence and extent of thrombus formation.

Materials and Methods

Ablation lesions were performed in 22 mongrel dogs at sites preselected by a randomized factorial design devised to compare RF ablation with cryocatheter configurations of varying sizes (7-French and 9-French), cooling rates (-1°C/s, -5 °C/s, and -20 °C/s), and target temperatures (-55°C and -75 °C). Lesions were created in the right atrium and both ventricles of each animal with one predetermined ablation setting per chamber (i.e. energy type, catheter size, cooling rate, and target temperature). Acetylsalicylic acid 325 mg/day was initiated seven days prior to ablation and continued until animal sacrifice. Dogs were anaesthetized with pentobarbital sodium (25 to 30 mg/kg), intubated, and ventilated with positive pressure Harvard respirators. An intravenous heparin bolus of 100 IU/kg was administered, followed by hourly injections of 15 IU/kg.

Sheath introducers were placed in the femoral artery and vein. In adherence to the protocol, a 7-French or 9-French cryocatheter (Freezor™, CryoCath Technologies Inc., Montreal, Canada) or 7-French quadripolar RF catheter (Biosense Webster, Inc., Diamond Bar, CA) with a 4-mm distal electrode tip was positioned under fluoroscopic guidance. Surface and intracardiac ECG recordings were displayed on a multichannel oscilloscope (Electronics for Medicine, VR-12, Honeywell Inc., Pleasantville, NY) and stored on a VHS tape recorder. Each cryoapplication was maintained for four minutes. Temperatures were displayed and recorded by a CryoCath console with ±1°C accuracy over the range of +40°C to -80°C at a sampling rate of 10/s. Average and maximum cooling rates and average and minimum temperatures were calculated using a customized Matlab program. RF ablations were maintained for 60 seconds at 50 Watts with a target temperature of +70°C. Maximum impedance and maximum and mean temperature and power were displayed on the generator (EP Technologies Inc., San Jose, CA).

Animals were sacrificed at seven days with a lethal injection of pentobarbital. Heart and lungs were explanted, rinsed, fixed in 10% formalin, and transferred to a pathology laboratory. All personnel were blinded to treatment modality. Representative photographs of epicardial and endocardial surfaces were taken and gross surface maximal lesion length and width measured. Tissues were dehydrated and paraffin embedded. Specimens were serially sectioned perpendicular to the endocardial surface in 1000 μm increments at a thickness of 6 μm with a motorized microtome (Olympus #4060E). Sections were stained with Masson's trichrome. A calibrated light microscope using Scion image 1.60 software for CG-7 (Scion Corp., Frederick, MD) was used for morphometric measurements of thrombus volume and lesion depth. Thrombus was defined as being present if its volume exceeded 0.1 mm^3.

Statistical Analyses

Given that several ablation lesions were created in each animal, all analyses took into consideration the non-independent nature of the data structure. For binary outcomes (e.g. presence or absence of thrombus) generalized estimating equations (GEE), which are robust to an assigned correlation configuration, were used to produce multiple regression marginal models for cluster sampling data by specifying link and distribution functions. For continuous outcomes (e.g. thrombus volume), both GEE and mixed regression models with pre-specified covariance matrix assumptions were used. Analyses were performed with and without potential outliers and influential observations. Two-tailed P-values<0.05 were considered statistically significant. Statistical testing was performed using SAS software Version 8 (SAS Institute, Cary, NC).

Results

Baseline Characteristics

A total of 197 RF and cryoenergy lesions were systematically created in the right atrium and both ventricles of 22 mongrel dogs (7 males, 15 females). Of these lesions, 176 (89.3%) were identified macroscopically and processed for histological analysis. Of the 21 missing lesions, 15 (71.4%) were created by 7-French cryocatheters, 2 (9.5%) by 9-French cryocatheters, and 4 (19.0%) by RF ablation. These lesions were uniformly dispersed within the right atrium (n=6), right (n=8) and left ventricles (n=7). Moreover, missing lesions created by 7-French cryocatheters were evenly distributed among the various ablation settings.

Subdivision of lesions according to energy modality, catheter size, and ablation parameters is depicted in Figure 1. No differences in the distribution of ablation site (Table 1) and gender of the animals were noted between cryoenergy and RF lesions. For reasons that remain unclear, one dog was unusually thrombogenic, with thrombus formation identified in 10 of 11 ablation sites involving both RF and cryoenergy. Statistical analyses performed with and without these lesions yielded similar results. Therefore, the following data includes all lesions.

Presence of Thrombus

Overall incidence of thrombus formation was 75.8% with RF and 30.1% with cryoablation (P=0.0005). An example of thrombus at the site of RF ablation is depicted in Figure 2. With the currently available 7-French cryocatheter, thrombus was observed in 24.2% of lesions. Radiofrequency energy remained a strong predictor of thrombus formation in a multivariate analysis controlling for site of ablation, gender, and lesion dimensions [OR 5.6, 95% CI (1.7, 18.4), *P*= 0.0042]. When cryolesions were considered separately, cryocatheter size (7-French versus 9-French), cooling rate, and target temperature did not predict thrombus formation. Similarly, an analysis of RF lesions found no correlation between RF ablation parameters (i.e. power, temperature, and impedance) and thrombus.

In univariate analyses of all ablation lesions, site of ablation and gender were not correlated with thrombus formation. Larger lesion dimensions were, however, associated with a higher incidence of thrombosis. This correlation was consistently found for area (P=0.0047), depth (P=0.0195), and volume (P=0.0111). In multivariate analyses, lesion volume but not area or depth remained an independent predictor of thrombus formation, with an OR of 1.014, 95% CI (1.002, 1.025) for a 1 mm^3 increase in volume (P= 0.0218).

Thrombus Volume

As depicted in Table 1, in multivariate analysis, thrombus volume was significantly greater with RF compared to all cryoenergy lesions (mean=5.4 mm^3, median=2.8 mm^3 versus mean= 0.8 mm^3, median=0.0 mm^3, P<0.0001). Significantly larger thrombi were noted when RF ablation was compared to both 7-French (mean=0.7 mm^3, median=0.0 mm^3, P<0.0001) and 9-French (mean=1.6 mm^3, median=0.5 mm^3, P=0.0002) cryolesions (Figure 3).

Independent predictors of thrombus volume for all lesions, RF, and cryolesions are summarized in Table 2. Similar to thrombus formation, lesion dimensions but not site of ablation or gender were associated with thrombus volume. Lesion area (P<0.0001), depth (P<0.0001), and volume (P<0.0001) were significantly positively correlated with thrombus volume. When RF lesions were considered separately, lesion dimensions remained independent predictors of thrombus volume. Moreover, lower average RF ablation temperatures were associated with larger thrombi (P=0.0008), in part explained by the strong relationship between higher average delivered power and lower temperature (P<0.0001).[8] In contrast, a subgroup analysis of all cryolesions revealed no association between lesion dimensions and thrombus volumes. The 9-French compared to 7-French cryocatheter was associated with thrombi that were, on average, 1.25 mm^3 larger (P=0.0413). Cryoenergy cooling rates and temperatures did not correlate with thrombus size.

Ablation Lesion Characteristics

Histologically, on qualitative analysis, cryolesions were well-circumscribed discrete lesions with sharp borders, dense areas of fibrotic tissue, and contraction band necrosis (see Figure 2). In contrast, RF lesions were characterized by intralesional hemorrhage and ragged edges less clearly demarcated from underlying normal myocardium. Moreover, replacement fibrosis confined to the outer margin of RF but not cryolesions suggests a slower post-ablation healing response to RF energy. Interestingly, lesions free of thrombus formation exhibited intact endothelial cell layers.

Radiofrequency ablation resulted in lesions of greater area (P=0.0018) and nearly significantly larger volume (P=0.0585) but not depth when compared to cryolesions. Cryolesion dimensions were of equal depth but of greater area (P=0.0305) and volume (P=0.0454) with 9-French compared to 7-French cryocatheters. Moreover, colder temperatures were associated with deeper lesions. For example, achieving a peak temperature 10°C colder resulted in an average lesion 0.38 mm deeper [95% CI (0.19, 0.57), P=0.0001]. Not unexpectedly, ventricular ablation lesions were deeper than their atrial counterparts ($P<0.0001$), with all atrial lesions being transmural. Lesion area and volume were not significantly associated with cooling rate, temperature, or ablation site.

Discussion

Since its first clinical use in 1986,[9] RF ablation has evolved as an effective nonpharmacologic therapy for a wide array of tachyarrhythmias. While the procedure carries a low risk of cardiovascular complications, thromboembolism is of concern. Though rare in otherwise healthy patients, thromboemboli may have devastating long-term consequences.[10]

Incidence of Thromboembolic Complications

The incidence of thrombus formation at the ablation site had not been previously well-defined. Employing DC energy ranging from 100-360J, Moro et al. reported a 20% incidence of thrombosis in mongrel dogs 7 days after ablation.[11] In the current study, thrombus was detected histologically in 75.8% of RF ablation sites. This high incidence reflects, in part, the enhanced detection capabilities of a sensitive morphometric analysis. While detected thrombi may indicate potential for systemic emboli, smaller lesions are probably not clinically significant, as symptomatic events are manifestly less common. In a study by Goli et al.,[12] thrombus was identified in 2 of 95 patients with routine transesophageal echocardiography following ablation, both of which were at sites remote from ablation lesions.

Several cases involving neurological,[2,10,13-15] pulmonary,[14,16] coronary,[17] and peripheral artery[14,18] thromboembolic complications following RF ablation have been reported. The incidence of such complications has been recently reviewed.[1] In the Multicenter European Radiofrequency Survey,[14] thromboembolic complications were reported in 33 of 4398 patients (0.8%). Patients with ventricular tachycardia ablation had a

2.8% incidence of thromboemboli. In exclusively left-sided ablations, Thakur et al.[15] and Epstein et al.[2] reported 2% and 1.8% embolic rates, respectively. The lower incidence in right-sided ablations has been attributed to the clinically silent nature of most small-to-moderate pulmonary emboli.[1] Consistent with this hypothesis, the present study reports an equal incidence of thrombus formation with right and left-sided ablations.

Mechanism of Thromboembolism after RF Ablation

While some authors believe that thromboembolic complications occur as a result of catheter manipulation and not ablation,[2,19,20] a study by Manolis et al.[21] found that D-dimer levels doubled following catheter manipulation but increased six-fold after ablation. A recent report described a lobulated 1-cm thrombus identified by transesophageal echocardiography attached to the right atrial septum at the ablation site.[22]

With RF ablation, events leading to thrombus formation are thought to be initiated by endothelial cell injury.[1] Endothelial cells are highly sensitive to injury and are damaged or destroyed by RF energy, despite selective applications.[23] When endothelium continuity is interrupted, anticoagulant properties are lost. Subendothelial components such as collagen, tissue factor, and von Willebrand's factor become exposed to circulating blood.[24] Consequently, platelet adhesion, activation, and thrombin production ensue. Given this proposed pathophysiological mechanism, it may be expected that thrombus size would be directly related to extent of RF tissue injury. Indeed, in the current study, when RF ablation lesions were analyzed separately, larger lesion dimensions were associated with more voluminous thrombi. A direct relationship between thrombus volume and embolic complications, though seemingly intuitive, remains to be demonstrated.

Cryoenergy Ablation and Thromboembolic Complications

The thromboembolic risk associated with RF ablation elicits the question of whether an alternative energy source may provide a safer profile. Similar to RF, both microwave and laser energy achieve endocardial ablation through heating and are, therefore, subject to the same inherent risks of thrombus formation.[1] In contrast, cryoenergy may be advantageous in that the tissue damage produced spares the endothelial lining.

The mechanism of cryoenergy tissue injury is highly complex and involves freeze/thaw effects, hemorrhage, inflammation, and replacement fibrosis.[6,25-27] The net result is tissue destruction with sharply delineated lesions that preserve underlying tissue and extracellular matrix architecture. Whether the theoretical advantage of maintaining intact endocardium translates into a lower incidence of thrombus formation had not been previously determined. In a multivariate analysis, the present study quantified a highly significant 5.6-fold lower risk of thrombus formation with cryoenergy compared to RF ablation. In contrast to RF ablation, no correlation between lesion dimensions and thrombus volume was noted with cryolesions. This provocative observation is consistent with different mechanisms of lesion formation, with a less clear relationship between cryoablation lesion size and extent of endothelial cell injury. A plausible clinically relevant corollary to this finding is that interventions requiring more extensive tissue destruction, such as procedures for atrial fibrillation and ventricular arrhythmias, may benefit most from the lower thrombogenic nature of cryoablation. Review of the literature on surgical cryoablation suggests a very low risk of thromboembolic complications.[28-32] In 118 patients undergoing surgical ablation of reentrant supraventricular arrhythmias[30] and 82 patients with ectopic atrial tachycardia,[31] no thromboembolic complications were reported.

In a series of 14 patients undergoing the Maze procedure for atrial fibrillation, one patient with Yamagushi disease had a small pulmonary embolus.[32] No thromboembolic complications were noted in Ferguson and Cox's[28] series of 100 consecutive patients undergoing the cryosurgical Maze procedure.

The larger thrombi resulting from 9-French compared to 7-French cryoablation could not be explained by the predictably larger lesion dimensions resulting from greater contact area and double freeze/thaw cycles.[33] Catheter-induced mechanical trauma sufficient to alter electrical properties and damage accessory pathways has been previously described.[34,35] It is theoretically possible, though not histologically quantified by this analysis, that larger cryocatheters produced a greater extent of mechanical trauma with endothelial disruption resulting in larger thrombi.

Prevention of Thromboembolic Complications

There is a disheartening lack of scientific evidence supporting strategies to prevent thromboembolic complications in patients undergoing catheter ablation. The fact that cryoablation is significantly less thrombogenic than RF ablation is a noteworthy finding in this regard. Neither procedure duration, number of RF applications, nor anticoagulation protocols have been associated with thromboembolic events.[22] In an initial study by Manolis et al.,[36] combination therapy with aspirin and ticlopidine reduced D-dimer levels post ablation. However, when 59 patients undergoing RF ablation were randomized to pretreatment with aspirin or ticlopidine, neither agent prevented the rise in D-dimer levels.[37] Intraprocedural heparin has likewise not been proven to reduce thromboembolic events, although its use seems reasonable particularly in patients undergoing ablation in left-sided chambers.[1] At present, there is no consensus on anticoagulation protocols for catheter ablation.

In a multicenter study comparing RF temperature versus power-controlled ablation modes,[3] catheter coagulum was lower with temperature monitoring. A reduction in thromboembolic events has not, however, been demonstrated. In Epstein et al.'s series,[2] temperature-controlled mode was used in ¾ of patients in whom thromboembolic complications occurred. Irrigated catheter technology may prove advantageous over temperature-controlled RF ablation by maintaining a cooler electrode-tissue interface, but its salutary effects remain to be demonstrated. Evidently, further studies are required to assess strategies aimed at reducing thromboembolic events.

Limitations

A large proportion of the 21 non-identified lesions (i.e. 71.4%) were created by 7-French cryocatheters. These lesions were more likely to be smaller in size and free of thrombus formation. Therefore, a selection bias was introduced at the time of analysis comparing cryolesions with RF ablation lesions as well as 7-French versus 9-French cryolesions. However, direction of bias is towards the null hypothesis, leading to underestimation of the true risk associated with RF versus cryoablation and 9-French versus 7-French cryocatheters. Secondly, initial recommendations for cryoablation involved double rather than single freeze/thaw cycles.[33] Single freeze/thaw cycles with 7-French catheters are emerging as the procedure of choice and were, therefore, compared to the original 9-French double freeze/thaw cycles.[38,39] Number of freeze/thaw cycles may potentially confound the relationship between catheter size and dimension of ablation lesions as well as thrombus volume. The study design does not permit dissociating effects of catheter size from number of freeze/thaw cycles. Nevertheless, conclusions regarding comparisons between 9-French and 7-French cryolesions remain valid, with the caveat that original versus newer protocols were utilized.

All dogs were sacrificed at seven days. As such, histological analyses were performed at one predetermined point in time. Potentially different latency periods between RF and cryoablation and thrombus formation were not considered. Given that tissue destruction, hemorrhage, and inflammation occur within the first 48 hours,[6] there was no a priori reason to suspect that cryoablation would result in a higher incidence of late (i.e. >7 days) thrombus formation. Finally, caution must be exerted in extrapolating animal studies to humans. While such research may provide useful information and define priorities for clinical studies, reliable quantitative estimates of human risk cannot be inferred.

Conclusion

For endocardial ablation lesions of equal size in equivalent cardiac chambers, ablation using RF energy confers a greater than fivefold increased risk of thrombus formation with larger thrombus volumes when compared to cryoenergy. Whereas extent of RF tissue injury is positively correlated with thrombus bulk, cryoenergy lesion size does not predict thrombus volume. This likely reflects the histological observation that cryoablation results in well-delineated discrete lesions with preservation of tissue ultrastructure including the endothelial cell layer. In contrast, RF lesions have serrated edges with more extensive endothelial cell destruction.

Acknowledgements

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Figure Legends

Figure 1 Distribution of ablation lesions.

Figure 2 This figure depicts typical histological characteristics one week after cryoenergy (Panel A) and RF ablation (Panel B) when stained with Masson's trichome and magnified 16-fold. Note the more homogeneous nature of the cryolesion with a smoother sharper demarcation from intact myocardium (Panel A). In contrast, the RF lesion is less well circumscribed with serrated edges (Panel B). The arrow indicates endocardial thrombus formation at the ablation site.

Figure 3 Thrombus volume with RF ablation, 7-French, and 9-French cryoablation.

TABLE 1. Characteristics according to ablation modality

	RF Ablation N=33	Cryoenergy Ablation N=143	P-value
Chamber	RA 33.3%	RA 32.6%	NS
	RV 33.3%	RV 34.0%	
	LV 33.3%	LV 33.3%	
Average temperature (°C)	66.8±5.5	-60.0±12.1	NA
Presence of thrombus	75.8%	30.1%	0.0005
Thrombus volume (mm^3)	2.8 (0.3,7.2)*	0.0 (0.0,0.4)*	<0.0001
Lesion volume (mm^3)	94.6 (64.2,229.3)*	43.2 (26.1,77.7)*	0.0585
Lesion depth (mm)	6.0±3.0	4.9±1.7	NS
Lesion area (mm^2)	42.0 (28.5,72.0)*	20.0 (12.0,25.5)*	0.0018

RA indicates right atrium; RV, right ventricle; LV, left ventricle; NS, not statistically significant; NA, not applicable.

Continuous normally distributed variables are expressed as mean±standard deviation

*Non-normally distributed variables are expressed as median value and interquartile range (25^{th},75^{th} percentile)

TABLE 2. Independent predictors of thrombus volume

Variable	β-coefficient±SE(β)	*P*-value
All ablation lesions		
Radiofrequency versus cryoablation	3.36±0.62	<0.0001
Lesion depth	0.69±0.12	<0.0001
Lesion area	0.03±0.01	<0.0001
Lesion volume	0.01±0.001	<0.0001
Radiofrequency ablation lesions		
Lesion depth	2.57 ± 0.01	<0.0001
Lesion area	0.03±0.01	0.0097
Lesion volume	0.01±0.001	<0.0001
Average RF ablation temperature	-0.47±0.14	0.0008
Cryoablation lesions		
9-French versus 7-French cryocatheter	1.25±0.61	0.0413

Figure 1. Distribution of ablation lesions

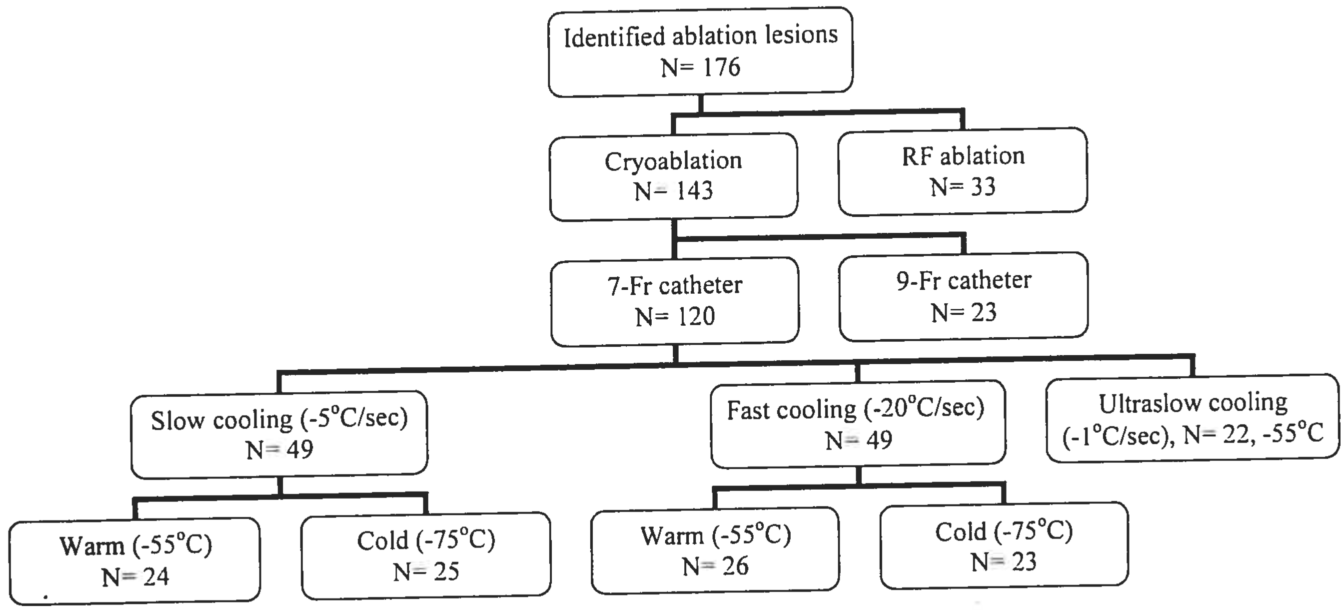


Figure 2. Histology of cryoenergy and RF lesions

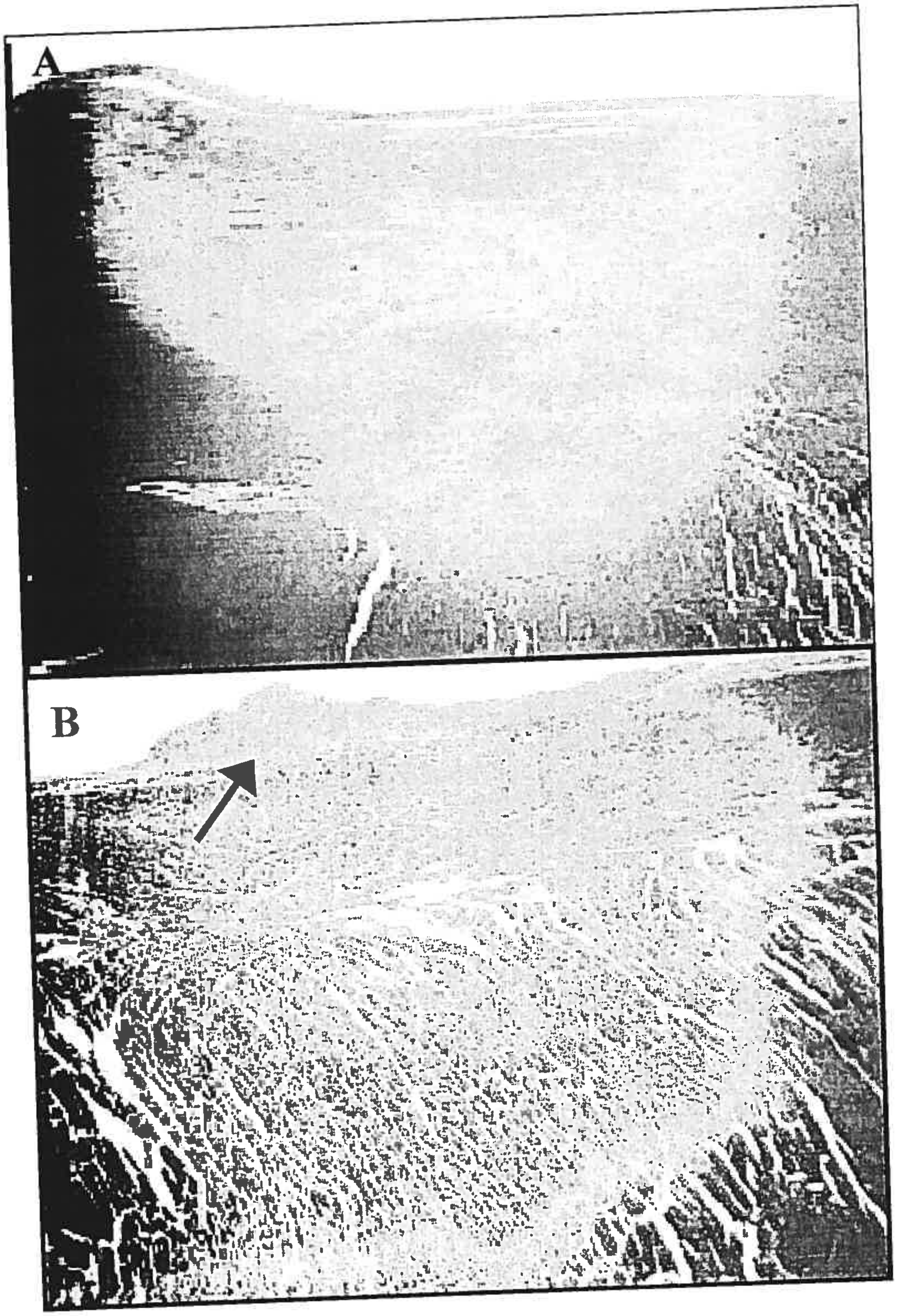
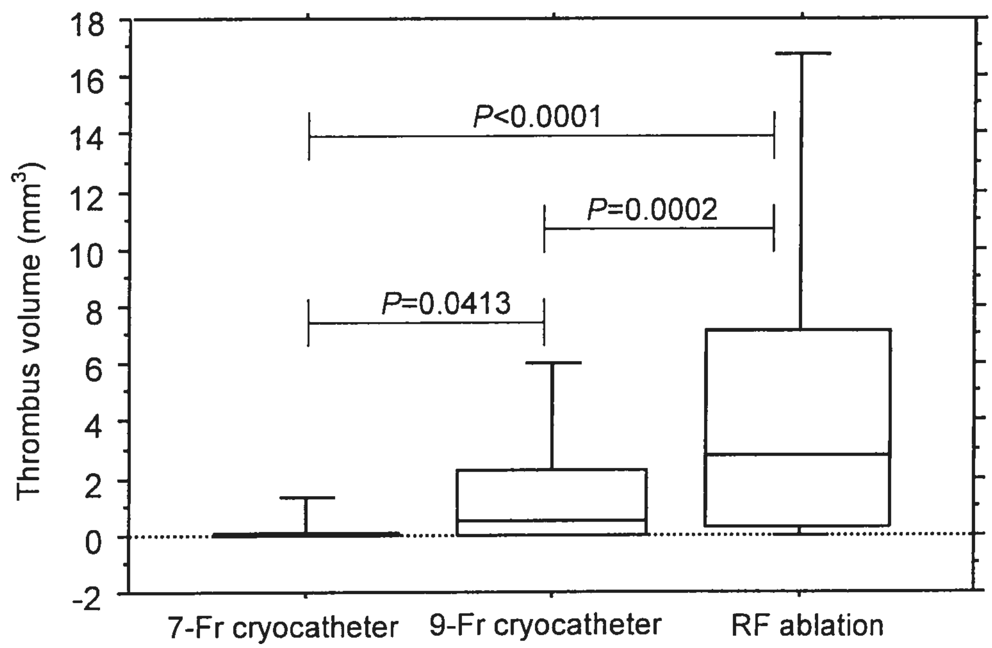


Figure 3. Thrombus volume with RF ablation and 7-French and 9-French cryoablation



Conclusion

Congenital heart disease patients represent a heterogeneous population with diverse underlying diagnoses. Improvements in surgical outcomes have given rise to a rapidly expanding population of young adult survivors. Arrhythmias and SCD appearing years after surgical repair figure prominently among complications that such patients face. The manuscripts presented in this thesis address some of the issues encountered in adult congenital electrophysiology.

Whereas prior studies relied on clinical parameters alone to risk stratify patients with tetralogy of Fallot, inducible VT on programmed ventricular stimulation was demonstrated to be a powerful predictor of clinical VT and SCD. Questions regarding patient selection for screening and the timing and frequency of testing remain to be elucidated. Studies are currently assessing whether risk assessment based on non-invasive parameters may be helpful in pre-selecting patients for further testing with programmed ventricular stimulation. For example, a multicenter case-control study spearheaded by the Pediatric Electrophysiology Society is attempting to generate a "risk score" for VT and SCD based on clinical, echocardiographic, and electrocardiographic parameters. This "risk score" may potentially be validated in the dataset created for this thesis, and then further refined to incorporate results of programmed ventricular stimulation. Studies addressing other angles of this complex issue are likewise being considered, including assessing the impact of ICDs on mortality in selected high-risk patients with tetralogy of Fallot.

Although often debated, disparities of outcomes in patients with D-TGA and Mustard versus Senning baffles remained speculative. The meta-analysis including 885 patients with Mustard and Senning procedures from seven studies suggests that there are indeed authentic differences between the two procedures, raising awareness for long-term follow-up. For example, patients with the Mustard procedure showed a trend towards lower mortality but exhibited more sinus node dysfunction. Data regarding atrial tachyarrhythmias were inconclusive. Much remains to be learned about the pathophysiology of SCD and risk factors for such in patients with atrial baffles for D-TGA. Research projects currently under consideration include a multi-center case-control study designed to explore associations between clinical variables and SCD. Also, a cohort study of ICD recipients with D-TGA that scrutinizes intracardiac recordings during appropriate ICD therapy may shed light on arrhythmic mechanisms that underlie their demise, e.g. supraventricular tachycardia that degenerates into a complex ventricular rhythm versus a primary ventricular arrhythmia. By better understanding substrates and risk factors for SCD, appropriate targeted preventive therapy may be instituted.

Finally, in a pre-clinical study, it was demonstrated that cryoenergy is less thrombogenic than RF energy. Although further research is required, this finding may be particularly relevant to adults with congenital heart disease. For example, in patients with congenital heart disease, extensive transcatheter ablation lesions may be necessary to interrupt complex and/or multiple atrial or ventricular macro-reentrant circuits. Moreover, otherwise clinically insignificant microthrombi that would have been directed towards the pulmonary circulation in patients with structurally normal hearts may, in the presence of congenital heart disease, be shunted to the systemic circulation and result in acute cerebrovascular accidents.

Clinical studies have yet to assess cryoablation in patients with congenital heart disease. It remains to be determined whether cryoablation lesions, like RF lesions, expand over time in growing hearts. Moreover, whereas inadequate thermodynamics may limit the formation of RF lesions in low flow states, such as those commonly encountered in congenital heart disease, conditions where warming effects of surrounding blood flow are lessened conversely promote cryolesion formation. Nevertheless, benefits of cryoablation in such congenital malformations remain to be demonstrated. Also, novel cryocatheter designs may likewise prove useful in creating extensive linear lesions necessary for the interruption of complex macro-reentrant circuits in congenital heart substrates.

The past decade has witnessed huge strides in our understanding of diagnostic and therapeutic options in adults with congenital heart disease. Nevertheless, SCD from presumed or documented arrhythmic events remains the most common cause of mortality. Clearly, research efforts directed towards better understanding cardiac electrophysiologic substrates, risk stratification, and improvements in arrhythmia management are warranted.

Appendix A: Coauthor consent forms

A) ***Declaration for coauthors of a manuscript:*** If a student is not the sole author of a manuscript that he/she wishes to include in his/her thesis, the student must obtain consent from all coauthors and attach a signed declaration of consent. A separate declaration must accompany each manuscript included in the thesis.

. **Student and program identification:**

Student name: Paul Khairy, MD, CM, MSc
Program: PhD, Biomedical Sciences (3-484-1-0)

2. **Description of the manuscript**

Title: Value of programmed ventricular stimulation after tetralogy of Fallot repair: a multicenter study; submitted to *Circulation*

Authors: Paul Khairy, Michael J. Landzberg, Michael A. Gatzoulis, Hugues Lucron, Jean Lambert, François Marçon, Mark E. Alexander, Edward P. Walsh

3. **Declaration of consent from all coauthors other than the student**

As a coauthor, I consent to having Paul Khairy include the manuscript cited above for his doctoral thesis entitled: "Adult congenital heart disease: long-term survival, arrhythmias, and emerging therapy".

[redacted]

Michael J. Landzberg — 7-31-03
Coauthor — Date

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Coauthor — Date

Jean Lambert — 8/03/04
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François Marçon — 3/03/04
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Mark E. Alexander — /03
Coauthor — Date

Edward P. Walsh — /29/03
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1. Student and program identification

Student name: Paul Khairy, MD, CM, MSc
Program: PhD, Biomedical Sciences (3-484-1-0), Faculty of Medicine

2. Description of the manuscript

Title: Long-term outcomes after atrial switch for transposition of the great arteries: a meta-analysis comparing Mustard and Senning procedures; submitted to *Cardiology in the Young*

Authors: Paul Khairy, Michael J. Landzbërg, Jean Lambert, Clare P. O'Donnell

3. Declaration of consent from all coauthors other than the student

As a coauthor, I consent to having Paul Khairy include the manuscript cited above for his doctoral thesis entitled: "Adult congenital heart disease: long-term survival, arrhythmias, and emerging therapy".

Michael J. Landzberg [redacted] 7-31-03
Coauthor Date

Jean Lambert 2/03/04
Coauthor Date

Clare P. O'Donnell 7-31-03.
Coauthor Date

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1. Student and program identification:

Student name: Paul Khairy, MD, CM, MSc
Program: PhD, Biomedical Sciences (3-484-1-0)

2. Description of the manuscript

Title: Lower incidence of thrombus formation with cryoenergy versus radiofrequency catheter ablation; Published in *Circulation* 2003; 107: 2045-2050.
Authors: Paul Khairy, Patrick Chauvet, John Lehmann, Jean Lambert, Laurent Macle, Jean-François Tanguay, Martin G. Sirois, Domenic Santoianni, Marc Dubuc

3. Declaration of consent from all coauthors other than the student

As a coauthor, I consent to having Paul Khairy include the manuscript cited above for his doctoral thesis entitled: "Adult congenital heart disease: long-term survival, arrhythmias, and emerging therapy".

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Date

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Domenic Santoianni [redacted] March 26, 2004
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FEE: None

RE: Khairy P, Landzberg MJ, Gatzoulis MA, Lucron H, Lambert J, Marçon F, Alexander ME, and Walsh EP. Value of programmed ventricular stimulation after tetralogy of Fallot repair: a multicenter study. Circulation 2004;109:1994-2000.

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From: Felicity Gil [F.Gil@ich.ucl.ac.uk] Sent: Mon 3/8/2004 12:04 PM
To: Khairy, Paul
Cc: [redacted]
Subject: RE: Card Young #03#160

Dear Dr Khairy,

re: Long-term outcomes after atrial switch. Ms# 03/160

Thank you for your message. We have now forwarded your manuscript to the publishers for processing, for inclusion in the June issue. You should receive the proofs direct from them, by e-mail, around the beginning of May.

Meanwhile, I am happy to grant you permission to include this manuscript in your PhD thesis.

Very best wishes,
Yours sincerely,
Robert H Anderson (sent on his behalf)

Copy: Gavin Jamieson, Greenwich Medical Media Ltd

Felicity Gil (Mrs)
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FEE: NONE

RE: Khairy P, Chauvet P, Lehmann J, Lambert J, Macle M, Tanguay J-F, Sirois MG, Santoianni D, and Dubuc M. Lower incidence of thrombus formation with cryothermal versus radiofrequency catheter ablation. Circulation 2003;107:2045-2050.

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Appendix C: Authorization to submit thesis by articles

Université de Montréal

Faculté des études supérieures
Vice-décanat

Le 1er avril 2004

Monsieur Paul Khairy
44, Longwood Avenue, app. 4
Brookline MA 02446
USA

Objet : Autorisation de déposer votre thèse de doctorat sous forme d'articles

Monsieur,

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Veuillez agréer, Monsieur, l'expression de mes sentiments les meilleurs.

Le vice-doyen,

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/vs

c.c. : M. Jean Lambert, directeur de recherche
M. Gilles Bleau, directeur des prog. Sc. Biomédicales

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Appendix D: Curriculum vitae

[redacted] [redacted]

PERSONAL INFORMATION:

Date of birth: April 20, 1971
Citizenship: Canadian
Marital status: Married (Nadine Yared)
Language capabilities: Fluent in English and French

EDUCATION:

2002-2004	Ph.D. Biomedical Sciences	Université de Montréal
2002-2004	Epidemiology and Biostiatistics	Harvard School of Public Health
1999-2002	M.Sc. Epidemiology and Biostatistics	McGill University, Montreal
1990-1995	M.D.,C.M.	McGill University, Montreal
1988-1990	D.E.C., Health Sciences	Marianopolis College, Montreal

POST-DOCTORAL TRAINING:

2003-2004	Pediatric/Congenital Electrophysiology, Senior Cardiology Fellow, Children's Hospital Boston, Harvard Medical School
2002-2003	Adult Congenital Heart Disease, Senior Cardiology Fellow, Brigham and Women's Hospital and Children's Hospital Boston, Harvard Medical School, Boston
2001-2002	Adult Electrophysiology, Senior Cardiology Fellow, Montreal Heart Institute, Montreal
1998-2001	Cardiology Fellow, Montreal Heart Institute, Montreal
1997-1998	Senior Resident, Internal Medicine, Sacré-Coeur Hospital, Montreal
1995-1997	Junior Resident, Internal Medicine, Notre-Dame Hospital, Montreal

UNIVERSITY AND HOSPITAL APPOINTMENTS:

2004/09	Assistant Professor of Medicine, Geographic Full-Time, Université de Montréal
2004/09	Assistant in Cardiology, Montreal Heart Institute, Montreal
2004/07	Assistant Professor of Medicine, Harvard Medical School
2004/07	Assistant in Cardiology, Children's Hospital Boston and Brigham and Women's Hospital, Harvard Medical School
2002-2004	Fellow in Pediatrics, Harvard Medical School
2002-2003	Instructor, Human Systems Pathophysiologic Course, Cardiovascular/Respiratory Block, Harvard Medical School
2001-2002	Chief fellow, Montreal Heart Institute
1998-1999	Chief resident, Montreal Heart Institute

LICENSURE AND CERTIFICATION:

2004/06	Subspecialty diploma, Pediatric Electrophysiology, Harvard University
2003/06	Subspecialty diploma, Adult Congenital Heart Disease, Harvard University
2002/07	Certificate of Limited Registration (#215295), Commonwealth of Massachusetts
2002/06	Subspecialty diploma, Electrophysiology, Montreal Heart Institute
2001/11	Subspecialty certification, Cardiology, American Board of Internal Medicine
2001/09	Subspecialty certification, Cardiology, Royal College of Physicians of Canada
2001/09	Specialist certificate, Cardiology, Corporation of Specialists of Quebec (CSPQ)
1999/06	Specialist, Internal Medicine, Royal College of Physicians of Canada (FRCPC)
1999/06	Specialist certificate in Internal Medicine, CSPQ
1998/10	American Board of Internal Medicine
1997/01	Licentiate of the Medical Council of Canada (LMCC)

ACADEMIC AND PROFESSIONAL EXPERIENCE:

2004/04 International Study Coordinator and Chair of Executive Committee, Septal Occluder ARrhythmia (SOAR) Study
2004/03 Secondary panel, Canadian cardiovascular consensus conference on atrial fibrillation
2003/10 Co-chair, Arrhythmia management in the patient with congenital heart disease, Canadian Cardiovascular Society Symposium, Toronto
2002- present Reviewer, American Board of Internal Medicine, Cardiovascular Exam
1998-1999, 2001-2002 Board of Directors, Montreal Heart Institute
1998-1999, 2001-2002 Education committee, Montreal Heart Institute
1998-1999, 2001-2002 Committee for Evaluation of Medical, Dental, and Pharmaceutical Acts, MHI
1998-1999, 2001-2002 Pharmacology Committee, Montreal Heart Institute
1998-1999, 2001-2002 Multidisciplinary Bioethics Committee, Montreal Heart Institute
1998-1999, 2001-2002 Library Committee, Montreal Heart Institute
1995-Present Class president, Medicine Class of 1995, McGill University

HONOURS AND AWARDS:

2004/09 Canada Research Chair, Université de Montréal
2003/11 Outstanding Research Award in Pediatric Cardiology, American Heart Association
2002-2004 Research Fellowship Scholarship, Canadian Institutes of Health Research
2002-2003 Detweiler Traveling Fellowship Scholarship, Royal College of Physicians and Surgeons of Canada
2002-2003 Fellowship Award, Pfizer, Inc. and the Association of Quebec Cardiologists
2002-2003 The Heart Gala Fellowship Scholarship, Montreal Heart Institute
2002 Clinical Research Project Award, Oral Presentation, Montreal Heart Institute
2000 Prize for Best Research Protocol, Department of Epidemiology and Biostatistics, McGill University
1999 Prize for Best Research Protocol, Department of Epidemiology and Biostatistics, McGill University
1991 Faculty Scholar, McGill University, Montreal
1990 R.E. Powell Major Scholarship, Awarded for Outstanding Academic Achievement and Leadership Qualities, McGill University, Montreal
1990 Marianopolis College Science Graduation Award, Highest Performance in Science Program
1990 Sister Mary MacCormack Scholarship, Top Four Students in Science Program, Marianopolis College
1989 Sister Mary MacCormack Scholarship, Top Four Students in Science Program, Marianopolis College
1988 Governor General's Medal, Highest Overall Average at Loyola High School, Montreal, Canada
1988 Marianopolis College Book Scholarship, for Outstanding Academic Achievement
1988 Chem 13 Award for Highest Score in National Chemistry Competition, University of Waterloo, Ontario
1988 Graduation prizes in Sciences, Mathematics, Chemistry, Physics, Economics, French, and Religion, Loyola High School

MEMBERSHIPS:

1995 Quebec Medical Association
1995 Canadian Medical Association
1998 Affiliate of the Quebec Association of Cardiologists
1998 Affiliate-in-training Canadian Cardiovascular Society
1998 Affiliate-in-training American College of Cardiology
1999 Corporation of Medical Specialists of Quebec
1999 Fellow of the Royal College of Physicians of Canada
2000 Affiliate-in-training North American Society of Pacing and Electrophysiology

REVIEWER:

Archives of Internal Medicine; Circulation; Heart; Journal of Interventional Cardiac Electrophysiology; Journal of the American College of Cardiology

PUBLICATIONS:

A) Published or In Press

1. **Khairy P** and Graham AF. Whipple's disease and the heart. Can J Cardiol 1996; 12 (9): 831-834.

2. **Khairy P** and Infante-Rivard C. Fulminant myocarditis. N Engl J Med 2000; 343 (4): 298-299.

3. Dubuc M, **Khairy P**, Rodriguez-Santiago A, Talajic M, Tardif J.-C., Thibault B, and Roy D. Catheter cryoablation of the atrioventricular node in patients with atrial fibrillation: a novel technology for ablation of cardiac arrhythmias. J Cardiovasc Electrophys 2001; 12: 439-444.

4. **Khairy P** and Marsolais P. Pancreatitis with electrocardiographic changes mimicking acute myocardial infarction. Can J Gastro 2001; 15 (8): 522-526.

5. Nattel S, **Khairy P**, and Schram G. Arrhythmogenic ionic remodeling: adaptive responses with maladaptive consequences. Trends in Cardiovasc Med 2001; 11(7): 295-301.

6. **Khairy P**. Coronary artery revascularization in patients with sustained ventricular arrhythmias in the chronic phase of a myocardial infarction. J Am Coll Cardiol 2001; 38 (4): 1268-1269.

7. **Khairy P**, Talajic M, Dominguez M, Tardif J.-C., Juneau M, Lavoie L, Roy D, and Dubuc M. Atrioventricular interval optimization and exercise tolerance. PACE 2001; 24: 1534-1540.

8. **Khairy P**, Guerra PG, Thibault B, Dubuc M, Roy D, and Talajic M. Alternating narrow and wide-complex tachycardia. PACE 2002; 25 (1): 103-4.

9. Nattel S, **Khairy P,** Roy D, Thibault B, Guerra PG, Talajic M, and Dubuc M. New approaches to atrial fibrillation management- a critical review of a rapidly-evolving field. Drugs 2002; 62 (16): 2377-2397.

10. **Khairy P** and Nattel S. New insights into the mechanisms and management of atrial fibrillation. CMAJ 2002; 167 (9): 1012-1020.

11. **Khairy P**, Chauvet P, Lehmann J, Lambert J, Macle M, Tanguay J-F, Sirois MG, Santoianni D, and Dubuc M. Lower incidence of thrombus formation with cryothermal versus radiofrequency catheter ablation. Circulation 2003; 107: 2045-2050.

12. **Khairy P,** Fournier A, and Dubuc M. Mönckeberg's sling. Can J Cardiol 2003;19 (6): 717-718.

13. **Khairy P**, Rinfret S, Tardif J-C, Marchand R, Shapiro S, Brophy J, and Dupuis J. Absence of association between infectious agents and endothelial function in healthy young men. Circulation 2003; 107: 1966-1971.

14. **Khairy P**, Thibault B, Talajic M, Dubuc M, Roy D, Guerra PG, and Nattel S. Prognostic significance of ventricular arrhythmias post myocardial infarction. Can J Cardiol 2003; 19 (12): 1393-1404.

15. **Khairy P,** O'Donnell CP, and Landzberg MJ. Systematic review and analysis of transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli. Annals of Internal Medicine 2003; 139: 753-760.

16. **Khairy P**, Rinfret S, Tardif J-C, Marchand R, Shapiro S, Brophy J, and Dupuis J. Infection, endothelial dysfunction, and atherogenesis. Circulation 2003; 108: 171e-172e.

17. Landzberg MJ and **Khairy P**. Indications for closure of patent foramen ovale. Heart 2004; 90: 219-224.

18. **Khairy P,** Landzberg MJ, Gatzoulis MA, Lucron H, Lambert J, Marçon F, and Walsh EP. Prognostic significance of electrophysiologic testing post tetralogy of Fallot repair: a multicenter study. Circulation 2004; 109: 1994-2000.

19. Noiseux N, **Khairy P**, Fournier A, and Vobecky SJ. Epicardial pacing in pediatric patients: 30 years of experience. Cardiol Young 2004; *In Press (August)*

20. **Khairy P**, Seslar SP, Triedman JK, and Cecchin F. Ablation of AV node reentrant tachycardia in tricuspid atresia. J Cardiovasc Electrophys 2004; *In Press (June)*

21. Fernandes SM, Sanders SP, **Khairy P**, Gauvreau K, Lang P, Simonds H, and Colan SD. Morphology of bicuspid aortic valve in children and adolescents. J Am Coll Cardiol 2004; *In Press*

22. **Khairy P**, Landzberg MJ, Lambert J, and O'Donnell CP. Long-term outcomes after atrial switch for transposition of the great arteries: a meta-analysis comparing Mustard and Senning procedures. Cardiol Young 2004; *In Press (June)*

B) Book Chapters

1. **Khairy P** and Dubuc M. Transcatheter cryoablation. *In*: Progress in Catheter Ablation: Clinical Application of New Mapping and Ablation Technology. Liem LM and Downar E (eds.): Kluwer Academic Publishers, The Netherlands, June 2002; Chapter 24: 389-408.

C) Abstracts

1. **Khairy P**, Talajic M, Dominguez M, Tardif J-C, Juneau M, Lavoie L, Dubuc M, and Roy D. Optimization of atrioventricular interval in patients with dual chamber pacemakers. Can J Cardiol 1996; 12 (Suppl E): 132E.

2. **Khairy P,** Rodriguez-Santiaga A, Talajic M, Tardif J-C, Thibault B, Roy D, and Dubuc M. Catheter cryoablation in man: early clinical experience. Can J Cardiol 1999; 15 (Suppl D): 173D.

3. **Khairy P**, Dubuc M, Guilbault E, Rodriguez-Santiago A, and Gallo R. Percutaneous cryoinjury induces neovascularization: a novel approach to myocardial revascularization. Can J Cardiol 1999; 15 (Suppl D): 129D-130D.

4. Rodriguez-Santiago A, **Khairy P**, Talajic M, Tardif J-C, Thibault B, Roy D, and Dubuc M. Catheter cryoablation in man: early clinical experience. Circulation 1999 (Suppl I); 100 (18): I-362.

5. **Khairy P**, Dubuc M, and Gallo R. Percutaneous cryoinjury induces neovascularization: a novel approach to myocardial revascularization. J Am Coll Cardiol 2000 (Suppl A); 35 (2): A5.

6. **Khairy P**, Rinfret S, Tardif J-C, Marchand R, Shapiro S, Brophy J, and Dupuis J. Absence of association between chlamydia pneumoniae, cytomegalovirus, Epstein-Barr virus and endothelial function. Can J Cardiol 2002; 18 (Suppl B): 182B.

7. **Khairy P** and Landzberg MJ. Systematic review and analysis of transcatheter closure versus medical therapy for patent foramen ovale. Circulation 2003; 107: e175.

8. Sturmer ML, de Lima GG, Ayala-Paredes F, **Khairy P**, Dubuc M, Roy D, Thibault B, Guerra PG, and Talajic M. Effect of pacing rate on arrhythmic events after atrio-ventricular nodal ablation. Can J Cardiol 2003; 19 (Suppl A): 217A.

9. **Khairy P**, Landzberg MJ, Gatzoulis MA, Lucron H, Lambert J, Marçon F, Alexander ME, and Walsh EP. Value of programmed ventricular stimulation after tetralogy of Fallot repair: a multicenter study. Can J Cardiol 2003; 19 (Suppl A): 203A-204A.

10. **Khairy P** and Landzberg MJ. Transcatheter device intervention versus medical therapy in the secondary prevention of cryptogenic stroke in patients with patent foramen ovale: systematic review and pooled analysis. Can J Cardiol 2003; 19 (Suppl A): 227A.

11. **Khairy P**, Landzberg MJ, Gatzoulis MA, Lucron H, Lambert J, Marçon F, Alexander ME, and Walsh EP. Prognostic significance of programmed ventricular stimulation after tetralogy of Fallot repair: a multicentre study. Circulation 2003; 107 (17): IV-375.